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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Sep 17	IMSworld Pharmaceutical Company Directory name change to PHARMASEARCH
NEWS 3	Oct 09	Korean abstracts now included in Derwent World Patents Index
NEWS 4	Oct 09	Number of Derwent World Patents Index updates increased
NEWS 5	Oct 15	Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS 6	Oct 22	Over 1 million reactions added to CASREACT
NEWS 7	Oct 22	DGENE GETSIM has been improved
NEWS 8	Oct 29	AAASD no longer available
NEWS 9	Nov 19	New Search Capabilities USPATFULL and USPAT2
NEWS 10	Nov 19	TOXCENTER(SM) - new toxicology file now available on STN
NEWS 11	Nov 29	COPPERLIT now available on STN
NEWS 12	Nov 29	DWPI revisions to NTIS and US Provisional Numbers
NEWS 13	Nov 30	Files VETU and VETB to have open access
NEWS 14	Dec 10	WPINDEX/WPIDS/WPIX New and Revised Manual Codes for 2002
NEWS 15	Dec 10	DGENE BLAST Homology Search
NEWS 16	Dec 17	WELDASEARCH now available on STN
NEWS 17	Dec 17	STANDARDS now available on STN
NEWS 18	Dec 17	New fields for DPCI
NEWS 19	Dec 19	CAS Roles modified
NEWS 20	Dec 19	1907-1946 data and page images added to CA and CAplus
NEWS 21	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
NEWS 22	Jan 25	Searching with the P indicator for Preparations
NEWS 23	Jan 29	FSTA has been reloaded and moves to weekly updates
NEWS 24	Feb 01	DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 25	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
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FILE 'HOME' ENTERED AT 10:54:23 ON 07 MAR 2002

=> File caplus BIOSIS
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FULL ESTIMATED COST                                         0.15       0.15

FILE 'CAPLUS' ENTERED AT 10:54:40 ON 07 MAR 2002
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FILE 'BIOSIS' ENTERED AT 10:54:40 ON 07 MAR 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

=> "herpes virus" (l) Vaccine
L1          396 "HERPES VIRUS" (L) VACCINE

=> intramuscular and L1
L2            7 INTRAMUSCULAR AND L1

=> "Candida species" (l) Vaccine
L3            1 "CANDIDA SPECIES" (L) VACCINE

=> Chlamydia (l) vaccine
L4          508 CHLAMYDIA (L) VACCINE

=> intramuscular and L4
L5           10 INTRAMUSCULAR AND L4

=> "Human papillomavirus" (l) vaccine
L6          659 "HUMAN PAPILLOMAVIRUS" (L) VACCINE

=> intramuscular and L6
L7            6 INTRAMUSCULAR AND L6

=> mycoplasmas (l) Vaccine
L8           36 MYCOPLASMAS (L) VACCINE

=> intramuscular and L8
L9            2 INTRAMUSCULAR AND L8

=> trepponema (w) pallidum (l) vaccine
L10           0 TREPPONEMA (W) PALLIDUM (L) VACCINE

=> gonococcal (l) immunity
L11          48 GONOCOCCAL (L) IMMUNITY

=> Gonococcal (l) Vaccine
L12         152 GONOCOCCAL (L) VACCINE

=> intramuscular and L12
L13           1 INTRAMUSCULAR AND L12

=> intramuscular and L11
L14           0 INTRAMUSCULAR AND L11

=> D L2 IBIB TI SO AU ABS 1-7
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L2 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:78095 BIOSIS
DOCUMENT NUMBER: PREV200200078095
TITLE: Duration of immunity induced by an adjuvanted and inactivated equine influenza, tetanus and equine herpesvirus 1 and 4 combination vaccine.
AUTHOR(S): Heldens, J. G. M. (1); Kersten, A. J.; Weststrate, M. W.; van den Hoven, R.
CORPORATE SOURCE: (1) Intervet International B.V., 5830 AA, Boxmeer Netherlands
SOURCE: Veterinary Quarterly, (November, 2001) Vol. 23, No. 4, pp. 210-217. print.
ISSN: 0165-2176.
DOCUMENT TYPE: Article
LANGUAGE: English
TI Duration of immunity induced by an adjuvanted and inactivated equine influenza, tetanus and equine herpesvirus 1 and 4 combination vaccine.
SO Veterinary Quarterly, (November, 2001) Vol. 23, No. 4, pp. 210-217. print.
ISSN: 0165-2176.
AU Heldens, J. G. M. (1); Kersten, A. J.; Weststrate, M. W.; van den Hoven, R.
AB An adjuvanted **vaccine** containing inactivated equine influenza, herpesvirus antigens, and tetanus toxoid was administered to young seronegative foals of 8 months of age by deep **intramuscular** injection in the neck (Group A). The first two vaccinations were given 4 weeks apart. The third was administered 6 months later. Another group of foals (Group B) was vaccinated according to the same scheme at the same time with monovalent equine **herpes virus** (EHV) **vaccine** (EHV1.4) **vaccine**. Antibody responses to the equine influenza (single radial haemolysis; SRH) and tetanus (ToBi ELISA) components of the **vaccines** were examined from first vaccination until 1 year after the third vaccination. The influenza components of the combination **vaccine** induced high antibody titres at two weeks after the second vaccination whereafter titres declined until the time of the third vaccination. After the third vaccination, the titres rose rapidly again to remain high for at least 1 year. Antibody titres against tetanus peaked only after the third vaccination but remained high enough to offer protective immunity for at least 1 year. Foals vaccinated with monovalent EHV1.4 remained seronegative for influenza and tetanus throughout the study. Four and a half months after the third vaccination of groups A and B, a third group of animals was vaccinated twice with monovalent EHV1.4 **vaccine** 4 weeks apart (Group C). Two weeks after the administration of the second dose in the later group, all groups (A, B, C and an unvaccinated control group D) were challenged with EHV-4. Vaccinated foals (Group A, B, C) showed a clear reduction of clinical symptoms and virus excretion after EHV-4 challenge compared with the unvaccinated control foals. No difference could be demonstrated among the vaccinated groups, suggesting that the combination **vaccine** protects as well as the monovalent **vaccine**. In EHV1.4-vaccinated foals both antigenic fractions induced clear protection up to 6 months after vaccination (9). It can therefore be anticipated that the efficacy of the combination **vaccine** against EHV-1 challenge is similar to the efficacy against EHV-1 induced by EHV1.4 vaccination.

L2 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:405073 BIOSIS
DOCUMENT NUMBER: PREV200000405073

TITLE: Analysis of latency in cattle after inoculation with a temperature sensitive mutant of bovine herpevirus 1 (RLB106.
AUTHOR(S): Jones, C. (1); Newby, T. J.; Holt, T.; Doster, A.; Stone, M.; Ciacci-Zanella, J.; Webster, C. J.; Jackwood, M. W.
CORPORATE SOURCE: (1) Department of Veterinary and Biomedical Science Center for Biotechnology, University of Nebraska, Lincoln, NE, 68583-0905 USA
SOURCE: Vaccine, (15 July, 2000) Vol. 18, No. 27, pp. 3185-3195. print.
ISSN: 0264-410X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Analysis of latency in cattle after inoculation with a temperature sensitive mutant of bovine herpevirus 1 (RLB106.
SO Vaccine, (15 July, 2000) Vol. 18, No. 27, pp. 3185-3195. print.
ISSN: 0264-410X.
AU Jones, C. (1); Newby, T. J.; Holt, T.; Doster, A.; Stone, M.; Ciacci-Zanella, J.; Webster, C. J.; Jackwood, M. W.
AB Calves were inoculated with the bovine **herpes virus** 1 (BHV-1) **vaccine** strain (RLB 106), which is a temperature sensitive mutant. The route of inoculation was intranasal instillation or **intramuscular** (IM) injection (flank or neck). As a control, five calves were given placebo by IM injection of the neck. Regardless of the infection route, clinical symptoms did not occur. However, BHV-1 neutralizing antibodies were detected after inoculation demonstrating that sero-conversion occurred. At 60 days post-inoculation, dexamethasone was given by IM injection to attempt reactivation of RLB 106. Only those calves inoculated by the intranasal route shed virus leading to an increase in BHV-1 specific antibodies. As expected, viral DNA and the latency related-RNA were detected in trigeminal ganglia (TG) of calves inoculated by the intranasal route. In contrast, viral nucleic acid was not detected in TG of calves inoculated by the IM route or in calves inoculated with placebo. In cervical ganglia or sacral dorsal root ganglia, viral nucleic acid was not consistently detected. This study provides evidence that efficient latency and reactivation does not occur following IM inoculation. Since serum-neutralizing antibodies were detected in all inoculated calves, IM inoculation led to sero-conversion.

L2 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:222822 BIOSIS
DOCUMENT NUMBER: PREV200000222822
TITLE: A gE-negative BHV1 vaccine virus strain cannot perpetuate in cattle populations.
AUTHOR(S): Mars, M. H. (1); de Jong, M.C.M.; van Oirschot, J. T.
CORPORATE SOURCE: (1) Department of Mammalian Virology, Institute for Animal Science and Health (ID-Lelystad), 8200 AB, Lelystad Netherlands
SOURCE: Vaccine, (April 14, 2000) Vol. 18, No. 20, pp. 2120-2124.
ISSN: 0264-410X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI A gE-negative BHV1 vaccine virus strain cannot perpetuate in cattle populations.
SO Vaccine, (April 14, 2000) Vol. 18, No. 20, pp. 2120-2124.
ISSN: 0264-410X.
AU Mars, M. H. (1); de Jong, M.C.M.; van Oirschot, J. T.

AB Three identical transmission experiments were successively performed to quantitatively evaluate the possible transmission of a gE-negative bovine herpesvirus 1 (BHV1) vaccine strain among cattle. After intranasal inoculation, the vaccine virus was excreted in high titers in nasal fluids. However, the vaccine virus was transmitted to only one sentinel in one experiment, and not to any of the 10 sentinel cattle in the other two experiments. Based on these observations, it can be concluded that the expected number of cases per vaccine-inoculated animal, i.e. the transmission ratio R0 of the vaccine strain, is significantly below 1. The R0 was estimated to be 0.14. After **intramuscular** inoculation, shedding of vaccine virus was not detected. Therefore, we concluded that it is highly unlikely that this live gE-negative BHV1 vaccine strain will perpetuate in the cattle population.

L2 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:519706 BIOSIS
DOCUMENT NUMBER: PREV199799818909
TITLE: Effect of microencapsulation on immunogenicity of a bovine herpes virus glycoprotein and inactivated influenza virus in mice.
AUTHOR(S): Moser, Charlotte A. (1); Speaker, Tully J.; Offit, Paul A.
CORPORATE SOURCE: (1) Section Infectious Diseases, Children's Hosp. Philadelphia, 34th St. and Civic Center Blvd., Philadelphia, PA 19104 USA
SOURCE: Vaccine, (1997) Vol. 15, No. 16, pp. 1767-1772. ISSN: 0264-410X.
DOCUMENT TYPE: Article
LANGUAGE: English
TI Effect of microencapsulation on immunogenicity of a bovine herpes virus glycoprotein and inactivated influenza virus in mice.
SO Vaccine, (1997) Vol. 15, No. 16, pp. 1767-1772. ISSN: 0264-410X.
AU Moser, Charlotte A. (1); Speaker, Tully J.; Offit, Paul A.
AB We previously found that aqueous-based spermine-alginate or spermine-chondroitin sulfate microcapsules enhanced rotavirus-specific humoral immune responses after **intramuscular** inoculation of mice. To extend our observations with whole, infectious rotavirus to **vaccine** strategies which include inactivated virus and purified proteins, we determined the capacity of aqueous-based microcapsules to enhance virus-specific immune responses to bovine **herpes virus** type 1 glycoprotein D (BHV-1-gD) or ether treated influenza virus. We found that spermine-alginate microcapsules decreased the quantity of BH-V-1-gD necessary to induce protein-specific antibodies about 5000-fold. However, spermine-alginate microcapsules did not enhance influenza virus-specific antibody responses. Microcapsules composed of spermine-chondroitin sulfate did not enhance either BHV-1-gD or influenza virus-specific immune responses. Possible mechanisms of enhancement of virus-specific antibody responses by microencapsulation are discussed.

L2 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:319778 BIOSIS
DOCUMENT NUMBER: PREV199799610266
TITLE: High level of transgene expression in cell cultures and in the mouse by replication-incompetent adenoviruses harboring modified VAI genes.
AUTHOR(S): Eloit, M. (1); Adam, M.; Gallais, I.; Fournier, A.
CORPORATE SOURCE: (1) Genetique Virale, Unite Genetique Moleculaire, INRA,

Ecole Natl. Veterinaire Alfort, 94704 Maisons Alfort France
SOURCE: Journal of Virology, (1997) Vol. 71, No. 7, pp. 5375-5381.
ISSN: 0022-538X.
DOCUMENT TYPE: Article
LANGUAGE: English
TI High level of transgene expression in cell cultures and in the mouse by replication-incompetent adenoviruses harboring modified VAI genes.
SO Journal of Virology, (1997) Vol. 71, No. 7, pp. 5375-5381.
ISSN: 0022-538X.
AU Eloit, M. (1); Adam, M.; Gallais, I.; Fournier, A.
AB Replication-incompetent adenoviruses are currently used in gene therapy trials. Most of the work designed to increase the expression from these vectors concerns the modification of cis sequences of the foreign transcription unit, so as to improve the transcription level or the stability of the mRNA. In this report, we show that an alternative strategy based on the coexpression of modified VAI genes can efficiently increase gene expression both in cell cultures and in animals. The VAI RNA is synthesized mainly during the late phase of the adenovirus cycle and increases the translation of late adenovirus gene products by counteracting the effect of an interferon-induced kinase, the PKR. We have constructed several modified VAI genes in which the central domain was deleted or substituted by exogenous sequences. These modified VAI genes, or the native VAI gene, were cloned into the left part of adenovirus type 5 genomes harboring their own endogenous VAI gene. One of the resulting viruses (Ad-VAr) increased 12.5- to 502-fold the expression level of reporter genes, either expressed as a constitutive cell line from an extrachromosomal DNA or introduced into cells by coinfection with another adenovirus vector. This effect was independent of the promoter, the coding sequence, and the 5' untranslated mRNA sequence and was obvious in the two non-E1-complementing cell lines tested (HeLa and Vero). Coinfection of Ad-VAr with adenoviruses expressing the luciferase gene from the major late promoter or Rous sarcoma virus (RSV) promoter by the intravenous route in mice increased by more than 33 (MLP)to 128 (RSV)- and 4,700 (MLP)- to 30,000 (RSV)-fold the expression level of the reporter gene in the lungs and liver, respectively. The **intramuscular** coinoculation of Ad-VAr and Ad-MLP-gD (a recombinant adenovirus **vaccine** expressing gD from the pseudorabies **herpes virus**) led to a 10-fold decrease in the protective dose of Ad-gD in mice. Ad-VAfull, a similar adenovirus in which the native VAI gene was cloned at the left part of the genome, showed no evidence of efficacy in cell culture and in mice. These results suggest that the use of modified VAI genes expressed at the early phase of the cycle can be helpful in the design of potent adenovirus vectors.

L2 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:109603 BIOSIS
DOCUMENT NUMBER: BA89:59094
TITLE: EFFICACY OF A LIVE PASTEURELLA-MULTOCIDA VACCINE FOR THE PREVENTION OF EXPERIMENTALLY INDUCED BOVINE PNEUMONIC PASTEURELLOSIS.
AUTHOR(S): CHENGAPPA M M; MCLAUGHLIN B G; KADEL W L; MADDUX R L; GREER S C
CORPORATE SOURCE: DEP. LAB. MED., COLL. VET. MED., KANSAS STATE UNIV.,

MANHATTAN, KANSAS 66506.
SOURCE: VET MICROBIOL, (1989) 21 (2), 147-154.
CODEN: VMICDQ. ISSN: 0378-1135.
FILE SEGMENT: BA; OLD
LANGUAGE: English
TI EFFICACY OF A LIVE PASTEURELLA-MULTOCIDA VACCINE FOR THE PREVENTION OF EXPERIMENTALLY INDUCED BOVINE PNEUMONIC PASTEURELLOSIS.
SO VET MICROBIOL, (1989) 21 (2), 147-154.
CODEN: VMICDQ. ISSN: 0378-1135.
AU CHENGAPPA M M; MCLAUGHLIN B G; KADEL W L; MADDUX R L; GREER S C
AB Seventeen Holstein-Friesian calves weighing an average of 139.8 .+-. 13.5 (mean .+-. standard deviation) kg were used in a study to determine the efficacy of a live **vaccine** containing of Pasteurella multocida A:3 and Pasteurella haemolytica A:1. Eleven calves received the **vaccine** by **intramuscular** injection in the right shoulder, whereas six calves received **vaccine** diluent and served as non-vaccinated controls. Fourteen days following vaccination (Day 15) all calves were inoculated deep intranasally with 3.6 .times. 107 TCID50 bovine **herpes virus**-1. On Day 16, calves were stressed by transports, and on Day 17 calves were challenged intratracheally with P. multocida A:3. On Day 22 calves were euthanized and necropsied, and tissues were collected for pathological and microbiological evaluations. Scores were assigned to each calf based on the severity of observed clinical signs. Macroscopic lung lesions were expressed as percentage of tissue involved relative to the total lung tissue of a calf. Plasma fibrinogen concentration, rectal temperature, serum antibody level, microscopic appearance of lung, and microbiologic results were also recorded for analyses. The control calves had significantly higher clinical-sign scores ($P < 0.05$) and more severe gross lesions ($P < 0.05$) than the vaccinated calves. Although the vaccinated calves had a slight increase of immunoglobulins M and G classes, the differences were not statistically significant ($P > 0.05$, $P > 0.05$). The results of the study indicate that the live Pasteurella **vaccine** is effective against experimental P. multocida infection in calves.

L2 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1986:220428 BIOSIS
DOCUMENT NUMBER: BA81:111728
TITLE: **INTRAMUSCULAR** AND INTRAVAGINAL VACCINATION OF PREGNANT COWS WITH THYMIDINE KINASE-NEGATIVE TEMPERATURE-RESISTANT INFECTIOUS BOVINE RHINOTRACHEITIS VIRUS BOVINE HERPESVIRUS 1.
AUTHOR(S): KIT S; KIT M; MCCONNELL S
CORPORATE SOURCE: DIVISION OF BIOCHEMICAL VIROLOGY, BAYLOR COLLEGE OF MEDICINE, HOUSTON, TEXAS USA.
SOURCE: VACCINE, (1986) 4 (1), 55-61.
CODEN: VACCDE. ISSN: 0264-410X.
FILE SEGMENT: BA; OLD
LANGUAGE: English
TI **INTRAMUSCULAR** AND INTRAVAGINAL VACCINATION OF PREGNANT COWS WITH THYMIDINE KINASE-NEGATIVE TEMPERATURE-RESISTANT INFECTIOUS BOVINE RHINOTRACHEITIS VIRUS BOVINE HERPESVIRUS 1.
SO VACCINE, (1986) 4 (1), 55-61.
CODEN: VACCDE. ISSN: 0264-410X.
AU KIT S; KIT M; MCCONNELL S
AB To test the safety and efficacy of a thymidine kinase-negative (TK-), temperature-resistant (TR) mutant of bovine **herpes virus** -1 (BHV-1) in pregnant cows, seronegative cows, 2-5 months pregnant, were vaccinated intramuscularly (i.m.) or intravaginally (i. vag.) with this candidate **vaccine** virus. I.m. vaccinated cows did not shed virus

i.vag. or intranasally (i.n.), but i.vag. vaccinated cows replicated virus
i.vag. for 8-9 days postvaccination (p.v.). some of the cows were challenge exposed i.n. at 46 days p.v. with virulent TK+ BHV-1(Cooper). Vaccinated cows showed no clinical disease signs p.v. or postchallenge and
responded anamnestically postchallenge. All cows delivered live calves. Pre-colostrum sera of the calves were negative for BHV-1 antibodies.

=> D L5 IBIB TI SO AU ABS 1-10

L5 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:346085 CAPLUS
DOCUMENT NUMBER: 135:75463
TITLE: Development of immune responses in mice to Chlamydia pneumoniae induced by **intramuscular** genetic vaccination
AUTHOR(S): Tharp, Anthony C.
CORPORATE SOURCE: Vanderbilt Univ., Nashville, TN, USA
SOURCE: (2000) 89 pp. Avail.: UMI, Order No. DA9970077 From: Diss. Abstr. Int., B 2000, 61(4), 1889
DOCUMENT TYPE: Dissertation
LANGUAGE: English
TI Development of immune responses in mice to Chlamydia pneumoniae induced by
intramuscular genetic vaccination
SO (2000) 89 pp. Avail.: UMI, Order No. DA9970077
From: Diss. Abstr. Int., B 2000, 61(4), 1889
AU Tharp, Anthony C.
AB Unavailable

L5 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:117105 CAPLUS
DOCUMENT NUMBER: 130:310349
TITLE: Characterization of immune responses following **intramuscular** DNA immunization with the MOMP gene of Chlamydia trachomatis mouse pneumonitis strain
AUTHOR(S): Zhang, D. J.; Yang, X.; Shen, C.; Brunham, R. C.
CORPORATE SOURCE: Department of Medical Microbiology, University of Manitoba, Winnipeg, Can.
SOURCE: Immunology (1999), 96(2), 314-321
CODEN: IMMUAM; ISSN: 0019-2805
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Characterization of immune responses following **intramuscular** DNA immunization with the MOMP gene of Chlamydia trachomatis mouse pneumonitis
strain
SO Immunology (1999), 96(2), 314-321
CODEN: IMMUAM; ISSN: 0019-2805
AU Zhang, D. J.; Yang, X.; Shen, C.; Brunham, R. C.
AB Studies were carried out to characterize the cellular and humoral immune responses evoked by i.m. DNA vaccination with the major outer membrane protein (MOMP) gene of Chlamydia trachomatis mouse pneumonitis strain. The data demonstrate that DNA vaccinated mice develop antigen-specific delayed-type hypersensitivity, lymphocyte proliferation and interferon-.gamma. (IFN-.gamma.) prodn. Serum antibody responses (mainly

IgG2a) were evoked in two-thirds of the mice. We conclude that i.m. DNA immunization with the MOMP gene evokes cellular and humoral (Th1) bias.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L5 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:431956 CAPLUS
DOCUMENT NUMBER: 127:175087
TITLE: **Intramuscular** immunization with a DNA **vaccine** produces partial immunity to **Chlamydia** trachomatis infection
AUTHOR(S): Zhang, Dong-Ji; Yang, Xi; Shen, Caixia; Berry, Jody; Mcclarty, Grant; Brunham, Robert C.
CORPORATE SOURCE: Department of Medical Microbiology, University of Manitoba, Winnipeg, MB, R3E 0W3, Can.
SOURCE: Vaccines 97: Mol. Approaches Control Infect. Dis., [Annu. Meet.], 14th (1997), Meeting Date 1996, 113-117. Editor(s): Brown, Fred. Cold Spring Harbor Laboratory Press: Cold Spring Harbor, N. Y. CODEN: 64QNAJ
DOCUMENT TYPE: Conference
LANGUAGE: English
TI **Intramuscular** immunization with a DNA **vaccine** produces partial immunity to **Chlamydia** trachomatis infection
SO Vaccines 97: Mol. Approaches Control Infect. Dis., [Annu. Meet.], 14th (1997), Meeting Date 1996, 113-117. Editor(s): Brown, Fred. Publisher: Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y. CODEN: 64QNAJ
AU Zhang, Dong-Ji; Yang, Xi; Shen, Caixia; Berry, Jody; Mcclarty, Grant; Brunham, Robert C.
AB The DNA-based immunization with the gene for the major surface protein of C. trachomatis (MOMP) but not with the gene for a cytoplasmic protein (CTP
synthetase) evoked protective immunity to lung infection with the C. trachomatis strain MoPN. The immunization was accompanied by the generation of elementary body-specific (EB) delayed-type hypersensitivity and low-titered serum antibodies to surface epitopes on EBs. However, immunity to infection was partial and less than that engendered by prior infection with MoPN or by immunization with heat-killed EBs.

L5 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:637506 CAPLUS
DOCUMENT NUMBER: 126:6438
TITLE: Vaccine compositions and method for enhancing an immune response
INVENTOR(S): Daynes, Raymond A.; Araneo, Barbara A.
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: U.S., 34 pp. Cont-in-part of U. S. Ser. No. 13,972, abandoned. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5562910	A	19961008	US 1993-123843	19930909

US 5827841	A	19981027	US 1994-295068	19940920
US 5753237	A	19980519	US 1994-309704	19940921
US 5919465	A	19990706	US 1994-309717	19940921
US 5837269	A	19981117	US 1995-487173	19950607

PRIORITY APPLN. INFO.:
US 1989-412270 19890925
US 1991-779499 19911018
US 1993-13972 19930204
US 1993-18471 19930216
US 1993-123843 19930909
US 1994-219418 19940329

OTHER SOURCE(S): MARPAT 126:6438

TI Vaccine compositions and method for enhancing an immune response

SO U.S., 34 pp. Cont-in-part of U. S. Ser. No. 13,972, abandoned.
CODEN: USXXAM

IN Daynes, Raymond A.; Araneo, Barbara A.

AB The invention relates to a vaccine which comprises an antigen and an immune response augmenting agent. The immune response augmenting agent is capable of enhancing T cell lymphokine prodn. Suitable immune response augmenting agents include, but are not limited to, dehydroepiandrosterone (DHEA) and DHEA-derivs. Examples of DHEA derivs. include DHEA-sulfate (DHEA-S), 16.alpha.-bromo-DHEA, 7-oxo-DHEA, 16.alpha.-bromo-DHEA-S and 7-oxo-DHEA-S. The invention also relates to a method for enhancing a vaccine-induced humoral immune response which comprises administering a vaccine which comprises an antigen and an immunomodulator. The immunomodulator may be an immune response augmenting agent, a lymphoid organ modifying agent or a mixt. of the immune response augmenting agent and lymphoid organ modifying agent. Suitable lymphoid organ modifying agents include, but are not limited to, 1,25-dihydroxy Vitamin D3, biol. active Vitamin D3 derivs. which are capable of activating the intracellular Vitamin D3 receptor, all trans-retinoic acid, retinoic acid derivs., retinol, retinol derivs. and glucocorticoid. Alternatively, the method for enhancing a vaccine-induced humoral immune response comprises sep. administering the immunomodulator and a vaccine contg. an antigen.

L5 ANSWER 5 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:94048 BIOSIS

DOCUMENT NUMBER: PREV200100094048

TITLE: Immunity to Chlamydia pneumoniae induced by vaccination with DNA vectors expressing a cytoplasmic protein (Hsp60) or outer membrane proteins (MOMP and Omp2.

AUTHOR(S): Penttila, Tuula (1); Vuola, Jenni M.; Puurula, Vuokko; Anttila, Marjukka; Sarvas, Matti; Rautonen, Nina; Makela, P. Helena; Puolakkainen, Mirja

CORPORATE SOURCE: (1) Department of Virology, Haartman Institute, University of Helsinki, FIN-00014, Helsinki: tuula.penttila@helsinki.fi Finland

SOURCE: Vaccine, (8 December, 2000) Vol. 19, No. 9-10, pp. 1256-1265. print.
ISSN: 0264-410X.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

TI Immunity to Chlamydia pneumoniae induced by vaccination with DNA vectors expressing a cytoplasmic protein (Hsp60) or outer membrane proteins (MOMP and Omp2.

SO Vaccine, (8 December, 2000) Vol. 19, No. 9-10, pp. 1256-1265. print.
ISSN: 0264-410X.

AU Penttila, Tuula (1); Vuola, Jenni M.; Puurula, Vuokko; Anttila, Marjukka; Sarvas, Matti; Rautonen, Nina; Makela, P. Helena; Puolakkainen, Mirja

AB Immune responses induced by **intramuscular** DNA immunization with **Chlamydia** pneumoniae genes coding for the major outer membrane protein (MOMP), cysteine-rich outer membrane protein 2 (Omp2) or the heat shock protein 60 (Hsp60) were studied. BALB/c mice were vaccinated intramuscularly three times at 3-week intervals and challenged intranasally 2 weeks after the last injection. Immunization with pmomp or phsp60 showed 1.2-1.5 log reduction in the mean lung bacterial counts after the challenge. Specific antibodies were detected only in sera of the mice immunized with pomp2 and phsp60. Although immunization with pomp2 resulted in a strong serum antibody response against Omp2 protein, it failed to protect the mice. Immunization with any of the three **vaccines** did not reduce the severity of histologically assessed pneumonia, but resulted in significantly higher lymphoid reaction in the lung indicating immunological memory.

L5 ANSWER 6 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:34228 BIOSIS
DOCUMENT NUMBER: PREV200000034228
TITLE: Transgene as **vaccine** for **chlamydia**.
AUTHOR(S): Brunham, Robert Conrad; Zhang, Dong-ji
SOURCE: American Heart Journal, (Nov., 1999) Vol. 138, No. 5 PART 2, pp. S519-S522.
ISSN: 0002-8703.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Transgene as **vaccine** for **chlamydia**.
SO American Heart Journal, (Nov., 1999) Vol. 138, No. 5 PART 2, pp. S519-S522.
ISSN: 0002-8703.
AU Brunham, Robert Conrad; Zhang, Dong-ji
AB Background We evaluated the potential utility of DNA immunization with the major outer membrane protein (MOMP) gene of **Chlamydia** trachomatis mouse pneumonitis (MoPn) strain for induction of protective immunity to chlamydial infection in mice. Methods and Results Groups of Balb/c mice were immunized with naked DNA intramuscularly or intranasally or with MOMP DNA-transfected Salmonella typhimurium delivery orally. Mice were challenged with MoPn through the pulmonary route to assay for protective immunity. All 3 routes of DNA immunization elicited protective immunity. Mucosal delivery appeared more efficacious than **intramuscular** delivery. Conclusions DNA immunization with the **chlamydia** MOMP gene may be suitable for **vaccine** development.

L5 ANSWER 7 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:506107 BIOSIS
DOCUMENT NUMBER: PREV199900506107
TITLE: Turkeys are protected from infection with Chlamydia psittaci by plasmid DNA vaccination against the major outer membrane protein.
AUTHOR(S): Vanrompay, D. (1); Cox, E.; Volckaert, G.; Goddeeris, B.
CORPORATE SOURCE: (1) Laboratory of Gene Technology, KULeuven, K. Mercierlaan 92, B-3001, Heverlee Belgium
SOURCE: Clinical and Experimental Immunology, (Oct., 1999) Vol. 118, No. 1, pp. 49-55.
ISSN: 0009-9104.

6218166B1 6197755 6149922 6123948 59155087

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Turkeys are protected from infection with Chlamydia psittaci by plasmid DNA vaccination against the major outer membrane protein.
SO Clinical and Experimental Immunology, (Oct., 1999) Vol. 118, No. 1, pp. 49-55.
ISSN: 0009-9104.
AU Vanrompay, D. (1); Cox, E.; Volckaert, G.; Goddeeris, B.
AB Plasmid DNA expressing the major outer membrane protein (MOMP) of an avian
Chlamydia psittaci serovar A strain has been tested for its ability to raise an immune response and induce protection against challenge with the same serovar. A combined parenteral (**intramuscular** injection) and mucosal route (DNA drops administered to the nares) of DNA inoculation
was compared with gene gun-based immunization. The gene gun delivery of pcDNA1/MOMP as well as the **intramuscular**-intranasal DNA delivery primed both T-helper and B cell memory, although rMOMP-expressing cells did not induce high antibody responses. Evidence for the priming of the memory was provided by the fact that the pcDNA1/MOMP inoculations raised antibodies belonging to the IgG and not IgM isotype. However, in response to challenge only five out of 15 vaccinated turkeys showed four-fold increases in serum IgG after challenge. By contrast, evidence for the priming of T cell memory in response to challenge was found in all vaccinated turkeys, as shown by the significantly heightened proliferative
responses of peripheral blood lymphocytes following vaccination. Both immunization methods produced similar serological and lymphocyte proliferative responses. Notwithstanding the immunization method, a significant level of protection was observed in all pcDNA1/MOMP-immunized turkeys. The efficacy of MOMP-based DNA vaccination as a means of preventing severe clinical signs, lesions and chlamydia excretion in a turkey model of C. psittaci infection was demonstrated.

L5 ANSWER 8 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:276034 BIOSIS
DOCUMENT NUMBER: PREV199900276034
TITLE: Immunization with a peptide corresponding to chlamydial heat shock protein 60 increases the humoral immune response
in C3H mice to a peptide representing variable domain 4 of the major outer membrane protein of Chlamydia trachomatis.
AUTHOR(S): Motin, Vladimir L.; de la Maza, Luis M.; Peterson, Ellena M. (1)
CORPORATE SOURCE: (1) Department of Pathology, University of California, Irvine, Medical Science Building, Room D440, Irvine, CA, 92697-4800 USA
SOURCE: Clinical and Diagnostic Laboratory Immunology, (May, 1999) Vol. 6, No. 3, pp. 356-363.
ISSN: 1071-412X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Immunization with a peptide corresponding to chlamydial heat shock protein
60 increases the humoral immune response in C3H mice to a peptide representing variable domain 4 of the major outer membrane protein of Chlamydia trachomatis.

SO Clinical and Diagnostic Laboratory Immunology, (May, 1999) Vol. 6, No. 3, pp. 356-363.
ISSN: 1071-412X.
AU Motin, Vladimir L.; de la Maza, Luis M.; Peterson, Ellena M. (1)
AB C3H (H-2k) mice are susceptible to a vaginal challenge with human strains of **Chlamydia** trachomatis and thus are a useful strain for testing potential **Chlamydia vaccine** candidates. However, C3H mice are fairly poor responders in terms of the level of antibody resulting from immunization with potential protective peptides representing variable domains (VDs) of the major outer membrane protein (MOMP). C57BL/6 (H-2b) mice, on the other hand, are moderately resistant to a vaginal challenge but are good responders to the chlamydial MOMP VDs.
Peptides representing universal T-cell helper epitopes were employed to determine whether the antibody response to a peptide representing VD4 of the MOMP, which has been shown to contain neutralizing epitopes, could be enhanced in C3H and C57 mice. Universal T-cell helper peptides from tetanus toxin, the pre-S2 region of hepatitis B virus, and the mouse heat shock protein 60, as well as the corresponding segment of the **Chlamydia** heat shock protein60 (hspct), were coadministered with the VD4 peptide. Peptides were coencapsulated in liposomes containing the adjuvant monophosphoryl lipid A and administered by using a combination of
mucosal and **intramuscular** injection. The only T-cell helper peptide that improved the immune response as judged by antibody level, in vitro neutralization assays, and T-cell proliferation was hspct. The response in the C57BL/6 strain was not significantly enhanced with hspct over levels achieved with VD4 alone; however, in C3H mice the levels of serum antibody to C. trachomatis increased to that seen in C57 mice. However, the molecular specificity and immunoglobulin subclass distribution differed from those of the C57 response, and the neutralizing
titers and T-cell proliferation responses were lower. In both strains of mice, titers of vaginal antibody to C. trachomatis were low. In summary, of the T-helper peptides used, only hspct significantly enhanced the immune response of C3H mice to the VD4 peptide, but it had only a modest effect on the immune response of C57 mice.

L5 ANSWER 9 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:487881 BIOSIS
DOCUMENT NUMBER: PREV199799787084
TITLE: DNA vaccination with the major outer-membrane protein gene induces acquired immunity to Chlamydia trachomatis (mouse pneumonitis) infection.
AUTHOR(S): Zhang, Dong-Ji; Yang, Xi; Berry, Jody; Shen, Caixia; McClarty, Grant; Brunham, Robert C. (1)
CORPORATE SOURCE: (1) Dep. Medical Microbiol., Univ. Manitoba, Room 543, 730 William Ave., Winnipeg, MB R3E 0W3 Canada
SOURCE: Journal of Infectious Diseases, (1997) Vol. 176, No. 4, pp.
1035-1040.
ISSN: 0022-1899.
DOCUMENT TYPE: Article
LANGUAGE: English
TI DNA vaccination with the major outer-membrane protein gene induces acquired immunity to Chlamydia trachomatis (mouse pneumonitis) infection.
SO Journal of Infectious Diseases, (1997) Vol. 176, No. 4, pp. 1035-1040.
ISSN: 0022-1899.
AU Zhang, Dong-Ji; Yang, Xi; Berry, Jody; Shen, Caixia; McClarty, Grant;

Brunham, Robert C. (1)

AB The efficacy of DNA vaccination for prevention of **Chlamydia** trachomatis infection was studied using the murine model of pneumonia induced by the mouse pneumonitis (MoPn) isolate of C. trachomatis. **Intramuscular** DNA immunization with two chlamydial genes, one that encodes the major outer-membrane protein (MOMP) and one that encodes a cytoplasmic enzyme (cytosine triphosphate (CTP) synthetase) were tested. The MOMP DNA **vaccine** but not the CTP synthetase DNA **vaccine** generated significant delayed-type hypersensitivity and serum antibodies to MoPn elementary bodies and reduced the peak growth of MoPn by gt 100-fold following lung challenge infection. MOMP DNA immunization suggests a new approach to **vaccine** development for prevention of human chlamydial infection.

L5 ANSWER 10 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:465342 BIOSIS
DOCUMENT NUMBER: PREV199799764545
TITLE: **Intramuscular** immunization with a DNA **vaccine** produces partial immunity to **Chlamydia** trachomatis infection.
AUTHOR(S): Zhang, Dong-Ji; Yang, Xi; Shen, Caixia; Berry, Jody; McClarty, Grant; Brunham, Robert C.
CORPORATE SOURCE: Dep. Med. Microbiology, Univ. Manitoba, Winnipeg, MB R3E 0W3 Canada
SOURCE: Brown, F. [Editor]; Burton, D. [Editor]; Doherty, P. [Editor]; Mekalanos, J. [Editor]. Vaccines (Cold Spring Harbor), (1997) Vol. 97, pp. 113-117. Vaccines (Cold Spring Harbor); Molecular approaches to the control of infectious diseases.
Publisher: Cold Spring Harbor Laboratory Press 10 Skyline Drive, Plainview, New York 11803, USA.
Meeting Info.: Fourteenth Annual Meeting on Modern Approaches to the Control of Infectious Diseases Cold Spring Harbor, New York, USA September 9-13, 1996
ISSN: 0899-4056. ISBN: 0-87969-516-1.
DOCUMENT TYPE: Book; Conference
LANGUAGE: English

TI **Intramuscular** immunization with a DNA **vaccine** produces partial immunity to **Chlamydia** trachomatis infection.

SO Brown, F. [Editor]; Burton, D. [Editor]; Doherty, P. [Editor]; Mekalanos, J. [Editor]. Vaccines (Cold Spring Harbor), (1997) Vol. 97, pp. 113-117. Vaccines (Cold Spring Harbor); Molecular approaches to the control of infectious diseases.
Publisher: Cold Spring Harbor Laboratory Press 10 Skyline Drive, Plainview, New York 11803, USA.
Meeting Info.: Fourteenth Annual Meeting on Modern Approaches to the Control of Infectious Diseases Cold Spring Harbor, New York, USA September 9-13, 1996
ISSN: 0899-4056. ISBN: 0-87969-516-1.

AU Zhang, Dong-Ji; Yang, Xi; Shen, Caixia; Berry, Jody; McClarty, Grant; Brunham, Robert C.

=> D L7 IBIB TI SO AU ABS 1-6

L7 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:303283 CAPLUS
DOCUMENT NUMBER: 133:72617

TITLE: **Intramuscular** administration of E7-transfected dendritic cells generates the most potent E7-specific anti-tumor immunity
AUTHOR(S): Wang, T.-L.; Ling, M.; Shih, I.-M.; Pham, T.; Pai, Si;
Lu, Z.; Kurman, R. J.; Pardoll, D. M.; Wu, T.-C.
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institution, Baltimore, MD, USA
SOURCE: Gene Ther. (2000), 7(9), 726-733
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

TI **Intramuscular** administration of E7-transfected dendritic cells generates the most potent E7-specific anti-tumor immunity

SO Gene Ther. (2000), 7(9), 726-733
CODEN: GETHEC; ISSN: 0969-7128

AU Wang, T.-L.; Ling, M.; Shih, I.-M.; Pham, T.; Pai, Si; Lu, Z.; Kurman, R. J.; Pardoll, D. M.; Wu, T.-C.

AB Dendritic cells (DCs) are highly efficient antigen-presenting cells capable of priming both cytotoxic and helper T cells in vivo. Recent studies have demonstrated the potential use of DCs that are modified to carry tumor-specific antigens in cancer **vaccines**. However, the optimal administration route of DC-based **vaccines** to generate the greatest anti-tumor effect remains to be detd. This study is aimed at comparing the levels of immune responses and anti-tumor effect generated through different administration routes of DC-based vaccination. We chose the E7 gene product of **human papillomavirus** (HPV) as the model antigen and generated a stable DC line (designated as DC-E7) that constitutively expresses the E7 gene. Among the three different routes of DC-E7 **vaccine** administration in a murine model, we found that i.m. administration generated the greatest anti-tumor immunity compared with s.c. and i.v. routes of administration. Furthermore, i.m. administration of DC-E7 elicited the highest levels of E7-specific antibody and greatest nos. of E7-specific CD4+ T helper and CD8+ T cell precursors. Our results indicate that the potency of DC-based **vaccines** depends on the specific route of administration and that i.m. administration of E7-transfected DCs generates the most potent E7-specific anti-tumor immunity.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:309281 BIOSIS
DOCUMENT NUMBER: PREV200100309281
TITLE: **Vaccine** regimen for prevention of sexually transmitted infections with **human papillomavirus** type 16.
AUTHOR(S): Kowalczyk, Dariusz W.; Wlazlo, Anthony P.; Shane, Sara; Ertl, Hildegund C. J. (1)
CORPORATE SOURCE: (1) Wistar Institute, 3601 Spruce Street, Philadelphia, PA, 19104: ertl@wistar.upenn.edu USA
SOURCE: Vaccine, (14 May, 2001) Vol. 19, No. 25-26, pp. 3583-3590. print.
ISSN: 0264-410X.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI **Vaccine** regimen for prevention of sexually transmitted infections with **human papillomavirus** type 16.
SO Vaccine, (14 May, 2001) Vol. 19, No. 25-26, pp. 3583-3590. print. ISSN: 0264-410X.
AU Kowalczyk, Dariusz W.; Wlazlo, Anthony P.; Shane, Sara; Ertl, Hildegund C. J. (1)
AB Protection to sexually transmitted infections with oncogenic **human papillomaviruses** (HPV) such as type 16 is thought to be provided by neutralizing antibodies directed to the major outer capsid protein, the L1 protein. A DNA **vaccine** and an E1-deleted adenoviral recombinant human strain 5, both expressing the L1 protein of HPV-16, were developed and shown to express L1 protein able to assemble into virus-like particles (VLPs). The **vaccines** used in a prime-boost regimen, with the DNA given intramuscularly (i.m.) for priming, followed by an intranasal (i.n.) booster immunization with the viral recombinant, induced antibodies to L1 in sera and in vaginal secretions.

L7 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:145046 BIOSIS
DOCUMENT NUMBER: PREV200100145046
TITLE: Safety and immunogenicity trial in adult volunteers of a **human papillomavirus** 16 L1 virus-like particle **vaccine**.
AUTHOR(S): Harro, Clayton D.; Pang, Yuk-Ying Susana; Roden, Richard B. S.; Hildesheim, Allan; Wang, Zhaohui; Reynolds, Mary Jane; Mast, T. Christopher; Robinson, Robin; Murphy, Brian R.; Karron, Ruth A.; Dillner, Joakim; Schiller, John T.; Lowy, Douglas R. (1)
CORPORATE SOURCE: (1) National Institutes of Health, Bldg. 36, Rm. 1D-32, Bethesda, MD, 20892: drl@helix.nih.gov USA
SOURCE: Journal of the National Cancer Institute (Bethesda), (February 21, 2001) Vol. 93, No. 4, pp. 284-292. print. ISSN: 0027-8874.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Safety and immunogenicity trial in adult volunteers of a **human papillomavirus** 16 L1 virus-like particle **vaccine**.
SO Journal of the National Cancer Institute (Bethesda), (February 21, 2001) Vol. 93, No. 4, pp. 284-292. print. ISSN: 0027-8874.
AU Harro, Clayton D.; Pang, Yuk-Ying Susana; Roden, Richard B. S.; Hildesheim, Allan; Wang, Zhaohui; Reynolds, Mary Jane; Mast, T. Christopher; Robinson, Robin; Murphy, Brian R.; Karron, Ruth A.; Dillner, Joakim; Schiller, John T.; Lowy, Douglas R. (1)
AB Background: Studies in animal models have shown that systemic immunization with a papillomavirus virus-like particle (VLP) **vaccine** composed of L1, a major structural viral protein, can confer protection against subsequent experimental challenge with the homologous virus. Here we report results of a double-blind, placebo-controlled, dose-escalation

trial to evaluate the safety and immunogenicity of a **human papillomavirus** (HPV) type 16 (HPV16) L1 VLP **vaccine** in healthy adults. Methods: Volunteers were given **intramuscular** injections with placebo or with 10- or 50-mug doses of HPV16 L1 VLP **vaccine** given without adjuvant or with alum or MF59 as adjuvants at 0, 1, and 4 months. All **vaccine** recipients were monitored for clinical signs and symptoms for 7 days after each inoculation. Immune responses were measured by an HPV16 L1 VLP-based enzyme-linked immunosorbent assay (ELISA) and by an HPV16 pseudovirion neutralization assay. The antibody titers were given as the reciprocals of the highest dilution showing positive reactivity in each assay. All statistical tests were two-sided. Results: The prevaccination geometric mean ELISA titer for six seropositive individuals was 202 (range, 40-640). All **vaccine** formulations were well tolerated, and all subjects receiving **vaccine** sero-converted. Serum antibody responses at 1 month after the third injection were dose dependent in recipients of **vaccine** without adjuvant or with MF59 but were similar at both doses when alum was the adjuvant. With the higher dose, the geometric means of serum ELISA antibody titers (95% confidence intervals) to purified VLP 1 month after the third injection were as follows: 10 240 (1499 to 69 938) without adjuvant, 10 240 (1114 to 94 145) with MF59, and 2190 (838 to 5723) with alum. Responses of subjects within each group were similar. Neutralizing and ELISA antibody titers were highly correlated (Spearman correlation = .85), confirming that ELISA titers are valid proxies for neutralizing antibodies. Conclusions: The HPV16 L1 VLP **vaccine** is well tolerated and is highly immunogenic even without adjuvant, with the majority of the recipients achieving serum antibody titers that were approximately 40-fold higher than what is observed in natural infection.

L7 ANSWER 4 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:468306 BIOSIS
DOCUMENT NUMBER: PREV200000468306
TITLE: Induction of mucosal immunity to HPV16 capsid protein by DNA priming and intranasal booster immunization with a replication-defective adenoviral recombinant.
AUTHOR(S): Kowalczyk, D. W. (1); Wlazlo, A. P. (1); Shane, S. (1); Ertl, H. C. J. (1)
CORPORATE SOURCE: (1) Wistar Institute, 3601 Spruce Street, Philadelphia, PA, 19104 2 USA
SOURCE: Immunology Letters, (September, 2000) Vol. 73, No. 2-3, pp. 272. print.
Meeting Info.: 24th European Immunology Meeting of the European Federation of Immunological Societies (EFIS) Poznan, Poland September 23-26, 2000 European Federation of Immunological Societies
. ISSN: 0165-2478.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Induction of mucosal immunity to HPV16 capsid protein by DNA priming and intranasal booster immunization with a replication-defective adenoviral recombinant.
SO Immunology Letters, (September, 2000) Vol. 73, No. 2-3, pp. 272. print.
Meeting Info.: 24th European Immunology Meeting of the European Federation

of Immunological Societies (EFIS) Poznan, Poland September 23-26, 2000 European Federation of Immunological Societies
. ISSN: 0165-2478.
AU Kowalczyk, D. W. (1); Wlazlo, A. P. (1); Shane, S. (1); Ertl, H. C. J. (1)

L7 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:462001 BIOSIS
DOCUMENT NUMBER: PREV200000462001
TITLE: Induction of CD8 T cells by vaccination with recombinant adenovirus expressing human papillomavirus type 16 E5 gene reduces tumor growth.
AUTHOR(S): Liu, Dai-Wei; Tsao, Yeou-Ping; Hsieh, Chang-Hsun; Hsieh, Jer-Tsong; Kung, John T.; Chiang, Chia-Lien; Huang, Shyh-Jer; Chen, Show-Li (1)
CORPORATE SOURCE: (1) Department of Microbiology and Immunology, National Defense Medical Center, Taipei Taiwan
SOURCE: Journal of Virology, (October, 2000) Vol. 74, No. 19, pp. 9083-9089. print.
ISSN: 0022-538X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Induction of CD8 T cells by vaccination with recombinant adenovirus expressing human papillomavirus type 16 E5 gene reduces tumor growth.
SO Journal of Virology, (October, 2000) Vol. 74, No. 19, pp. 9083-9089. print.
ISSN: 0022-538X.
AU Liu, Dai-Wei; Tsao, Yeou-Ping; Hsieh, Chang-Hsun; Hsieh, Jer-Tsong; Kung, John T.; Chiang, Chia-Lien; Huang, Shyh-Jer; Chen, Show-Li (1)
AB The potential of the E5 protein as a tumor **vaccine** candidate has not been explored yet. In this study, we evaluate the **human papillomavirus** type 16 (HPV-16) E5 protein delivered by an adenovirus vector as a tumor **vaccine** for cervical lesions. The results demonstrate that a single **intramuscular** injection of a recombinant adenovirus carrying the HPV-16 E5 gene into syngeneic animals can reduce the growth of tumors which contain E5 gene expression. Moreover, the E5 **vaccine**-induced tumor protection occurs through CD8 T cells but not through CD4 T cells in in vitro assays. In addition, our studies using knockout mice with distinct T-cell deficiencies confirm that cytotoxic T-lymphocyte-induced tumor protection is CD8 dependent but CD4 independent. Hence, HPV-16 E5 can be regarded as a tumor rejection antigen.

L7 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:261858 BIOSIS
DOCUMENT NUMBER: PREV200000261858
TITLE: **Intramuscular** administration of E7-transfected dendritic cells generates the most potent E7-specific anti-tumor immunity.
AUTHOR(S): Wang, T.-L.; Ling, M.; Shih, I.-M.; Pham, T.; Pai, S. I.; Lu, Z.; Kurman, R. J.; Pardoll, D. M.; Wu, T.-C. (1)
CORPORATE SOURCE: (1) Department of Pathology, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD, 21287 USA
SOURCE: Gene Therapy, (May, 2000) Vol. 7, No. 9, pp. 726-733. print..
ISSN: 0969-7128.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

TI **Intramuscular** administration of E7-transfected dendritic cells generates the most potent E7-specific anti-tumor immunity.
SO Gene Therapy, (May, 2000) Vol. 7, No. 9, pp. 726-733. print..
ISSN: 0969-7128.
AU Wang, T.-L.; Ling, M.; Shih, I.-M.; Pham, T.; Pai, S. I.; Lu, Z.; Kurman, R. J.; Pardoll, D. M.; Wu, T.-C. (1)
AB Dendritic cells (DCs) are highly efficient antigen-presenting cells capable of priming both cytotoxic and helper T cells in vivo. Recent studies have demonstrated the potential use of DCs that are modified to carry tumor-specific antigens in cancer **vaccines**. However, the optimal administration route of DC-based **vaccines** to generate the greatest anti-tumor effect remains to be determined. This study is aimed at comparing the levels of immune responses and anti-tumor effect generated through different administration routes of DC-based vaccination.
We chose the E7 gene product of **human papillomavirus** (HPV) as the model antigen and generated a stable DC line (designated as DC-E7) that constitutively expresses the E7 gene. Among the three different routes of DC-E7 **vaccine** administration in a murine model, we found that **intramuscular** administration generated the greatest anti-tumor immunity compared with subcutaneous and intravenous routes of administration. Furthermore, **intramuscular** administration of DC-E7 elicited the highest levels of E7-specific antibody and greatest numbers of E7-specific CD4+ T helper and CD8+ T cell
precursors. Our results indicate that the potency of DC-based **vaccines** depends on the specific route of administration and that **intramuscular** administration of E7-transfected DCs generates the most potent E7-specific anti-tumor immunity.

=> D L9 IBIB TI SO AU ABS 102
2 ANSWERS ARE AVAILABLE. SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE
The answer numbers requested are not in the answer set.
ENTER ANSWER NUMBER OR RANGE (1):1-2

L9 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:312686 BIOSIS
DOCUMENT NUMBER: PREV199799620489
TITLE: Control of avian mycoplasmoses by vaccination.
AUTHOR(S): Whithear, K. G.
CORPORATE SOURCE: Dep. Vet. Sci., Vet. Clinical Centre, Univ. Melbourne, Princes Highway, Werribee, VIC 3030 Australia
SOURCE: Revue Scientifique et Technique Office International des Epizooties, Vol. 15, No. 4, pp. 1527-1553.
ISSN: 0253-1933.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English; French; Spanish
TI Control of avian mycoplasmoses by vaccination.
SO Revue Scientifique et Technique Office International des Epizooties, Vol. 15, No. 4, pp. 1527-1553.
ISSN: 0253-1933.
AU Whithear, K. G.
AB Vaccination is an option for controlling Mycoplasma gallisepticum or M. synoviae when biosecurity measures fail to prevent the infection of poultry flocks with these **mycoplasmas**. Both killed **vaccines** (bacterins) and living **vaccines** are currently in commercial use. Bacterins usually contain an oil emulsion adjuvant and

are administered by subcutaneous or **intramuscular** injection. They can reduce the decline in egg production associated with M. gallisepticum, although they do not prevent infection. Newer adjuvants, such as immune stimulating complexes, may provide effective immunity without the tissue lesions caused by oil emulsion adjuvants. Living M. gallisepticum **vaccines** include the F strain and attenuated strains ts-11 and 6/85. F strain is administered in drinking water or by aerosol. This strain reduces the decline in egg production and has been used to displace endemic strains in multiple-age flocks. The major disadvantage is the inherent virulence of F strain. Strain ts-11 is less virulent and less infectious than F strain and provides a somewhat weaker, but usually effective, long-term protective immunity, which is **vaccine**-dose dependent. This strain is administered bv eye drop, persists in the chicken for long periods and stimulates a detectable although variable systemic antibody response. Strain ts-11 can be used safely in combination with respiratory virus **vaccines**. Strain 6/85 also stimulates a weaker protective immune response than F strain and is of low virulence and infectivity. This strain is administered by aerosol, appears not to persist in vaccinated birds and may fail to stimulate a detectable systemic antibody response. Strain MS-H is currently being evaluated as a live **vaccine** against M. synoviae in meat chicken breeder flocks and is often used in conjunction with strain ts-11.

L9 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:18157 BIOSIS
DOCUMENT NUMBER: PREV199497031157
TITLE: Aerosol vaccination of pigs against Mycoplasma hyopneumoniae infection.
AUTHOR(S): Murphy, Duane Alva (1); Van Alstine, William George (1); Clark, L. Kirk; Albregts, Sharon
CORPORATE SOURCE: (1) Dep. Vet. Pathol., Purdue Univ., West Lafayette, IN 47907 USA
SOURCE: American Journal of Veterinary Research, (1993) Vol. 54, No. 11, pp. 1874-1880.
ISSN: 0002-9645.
DOCUMENT TYPE: Article
LANGUAGE: English
TI Aerosol vaccination of pigs against Mycoplasma hyopneumoniae infection.
SO American Journal of Veterinary Research, (1993) Vol. 54, No. 11, pp. 1874-1880.
ISSN: 0002-9645.
AU Murphy, Duane Alva (1); Van Alstine, William George (1); Clark, L. Kirk; Albregts, Sharon
AB Aerosol vaccination is used effectively to immunize poultry against Newcastle disease, but to the authors' knowledge, this vaccination procedure is not well studied in other species. The efficacy of IM and aerosol vaccination of pigs against Mycoplasma hyopneumoniae infection was evaluated. Twenty-one pigs from a Mycoplasma-free herd were randomly allotted by litter and body weight into 3 groups. One group was given aerosolized phosphate-buffered saline solution (PBSS) by inhalation. The second group (AERO) was given aerosolized M. hyopneumoniae **vaccine** by inhalation. The third group (IM) was given the same **vaccine** by IM injection. Vaccination by IM administration was repeated once, and aerosol vaccination was repeated twice at 2-week intervals. Two weeks after the last vaccination, all pigs were intratracheally challenge-exposed with 3 ml of broth culture containing 10-7

color-changing units (CCU) of a low-passage strain of virulent M. hyopneumoniae. Pigs were observed daily for coughing. Four weeks after challenge exposure, all pigs were necropsied. Percentage of lung affected by gross pneumonia was measured, bronchioalveolar lavage fluid (BALF) cells were counted, and quantitative culture for **mycoplasmas** was performed on lung sections. Additionally, M. hyopneumoniae-specific antibodies were measured in prevaccination, postvaccination, and postchallenge-exposure serum and BALF by use of indirect ELISA. Mean prevalence of persistent coughing in pigs of the AERO group (4.6 d/pig) was not different from that in pigs of the PBSS group (3.7 d/pig). Prevalence of coughing in IM vaccinated pigs (1.0 d/pig) was lower (P lt 0.05) than that in pigs of the PBSS group. Mean gross lung lesion scores and BALF cell counts were not different between the AERO (15% pneumonia, 5,233 cells/mu-l) and PBSS (11% pneumonia, 3,022 cells/mu-l) groups, but were lower (P lt 0.05) in the IM group (1.5% pneumonia, 400 cells/mu-l) than in the PBSS group. Mean lung mycoplasmal counts were not significantly (P lt 0.05) different among the PBSS (10-5.6 CCU/g), AERO (10-5.3 CCU/g), and IM (10-3.3 CCU/g) groups. Postvaccination M. hyopneumoniae-specific IgG or IgA was not detectable in BALF after either vaccination procedure. Postvaccination M. hyopneumoniae-specific serum IgG concentration was not different among the 3 groups. Postchallenge exposure M. hyopneumoniae-specific IgG and IgA were detectable in BALF of all pigs, but were not different among the 3 treatment groups. Postchallenge exposure-specific serum IgG concentration was not different between the PBSS (mean OD, 0.739) and AERO (mean OD, 0.672) groups, but was higher (P lt 0.05) in the IM group (mean OD, 1.185) than in the PBSS group. Aerosol vaccination failed to induce local and systemic antibody responses detectable by ELISA, and failed to protect pigs against mycoplasmal pneumonia. **Intramuscular** vaccination failed to induce local and systemic antibody responses detectable by ELISA, but substantially reduced the clinical signs and lesions caused by challenge exposure to virulent M. hyopneumoniae.

=> D L13 IBIB TI SO AU ABS

L13 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:179100 BIOSIS
DOCUMENT NUMBER: PREV199497192100
TITLE: Human experimentation with Neisseria gonorrhoeae: Rationale, methods, and implications for the biology of infection and vaccine development.
AUTHOR(S): Cohen, Myron S. (1); Cannon, Janne G.; Jerse, Ann E.; Charniga, Larry M.; Isbey, Susan F.; Whicker, Leesa G.
CORPORATE SOURCE: (1) Div. Infectious Dis., CB No. 7030, 547 Burnett-Womack, Univ. North Carolina, Chapel Hill, NC 27599 USA
SOURCE: Journal of Infectious Diseases, (1994) Vol. 169, No. 3, pp. 532-537.
ISSN: 0022-1899.
DOCUMENT TYPE: Article
LANGUAGE: English
TI Human experimentation with Neisseria gonorrhoeae: Rationale, methods, and implications for the biology of infection and vaccine development.
SO Journal of Infectious Diseases, (1994) Vol. 169, No. 3, pp. 532-537.

ISSN: 0022-1899.
AU Cohen, Myron S. (1); Cannon, Janne G.; Jerse, Ann E.; Charniga, Larry M.; Isbey, Susan F.; Whicker, Leesa G.
AB Neisseria gonorrhoeae infection is limited to the human host. Experimental urethral infection in male volunteers was used to study different aspects of the infection. Urethral installation of a variety of **gonococcal** variants (10-4-10-6) led to infection in 27 subjects, who developed pyuria and shed bacteria in urine before urethritis developed 1-6 days after **gonococcal** inoculation. The incubation period was affected by the inoculation procedure and size of the inoculum. Subjects were treated with **intramuscular** ceftriaxone (250 mg) if urethritis developed or at 6 days after inoculation. Urine cultures became negative within several hours of therapy, and symptoms resolved within 1 day of therapy. Infected patients suffered no major complications. Experimental male urethral **gonococcal** infection provides a unique opportunity to understand the biology and immunology of **gonococcal** infection and is an efficient method to test **gonococcal vaccine** candidates.

=> Immuneresponse (L) gonococcal (w) antigen
L15 0 IMMUNERESPONSE (L) GONOCOCCAL (W) ANTIGEN

=> Gonococcal (l) treatment
L16 723 GONOCOCCAL (L) TREATMENT

=> goconoccal (w) antigen
L17 0 GOCONOCCAL (W) ANTIGEN

=> immunogen and L16
L18 2 IMMUNOGEN AND L16

=> D L18 IBIB TI SO AU ABS 1-2

L18 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1980:424136 CAPLUS
DOCUMENT NUMBER: 93:24136
TITLE: Immunogenicity of ribosomal preparations from Neisseria gonorrhoeae
AUTHOR(S): Cooper, Morris D.; Tewari, Ram P.; Bowser, Dean V.
CORPORATE SOURCE: Sch. Med., South. Illinois Univ., Springfield, IL, 62708, USA
SOURCE: Infect. Immun. (1980), 28(1), 92-100
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Immunogenicity of ribosomal preparations from Neisseria gonorrhoeae
SO Infect. Immun. (1980), 28(1), 92-100
CODEN: INFIBR; ISSN: 0019-9567
AU Cooper, Morris D.; Tewari, Ram P.; Bowser, Dean V.
AB Protection against **gonococcal** infection was obtained by immunization with ribosomal prepns. from N. gonorrhoeae. Ribosomes were isolated from disrupted cells by differential ultracentrifugation and **treatment** of the microsomal fraction with 0.25% Na dodecyl sulfate. The isolated ribosomal prepns. contained 55% RNA, 39% protein, and 0.35% carbohydrate. The ribosomal prepns. contained small amts. of endotoxin as detd. by thiobarbituric acid- and lead acetate-sensitized

mice assays. Guinea pigs immunized s.c. with ribosomal prepns. were challenged intrachamberially with 107 colony-forming units of N. gonorrhoeae, and protection was assessed by clearance of the organism from s.c. chambers. The ribosomal prepns. elicited significant protection, which was enhanced by incorporation of the **immunogen** into adjuvant. This protection was comparable to that obtained with whole cells. **Treatment** with proteolytic enzymes destroyed the protective effect of the ribosomal prepns., but RNase had no measurable effect. Passive hemagglutination and immunodiffusion tests with serums from immunized animals demonstrated the presence of antibody to the ribosomal antigens. Adsorption of antiribosomal serums with enzyme-treated ribosomal prepns. also indicated the protein nature of the **immunogen**. Thus, protein assocd. with the **gonococcal** ribosomal prepn. is the major protective **immunogen**.

L18 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1980:251471 BIOSIS
DOCUMENT NUMBER: BA70:43967
TITLE: IMMUNOGENICITY OF RIBOSOMAL PREPARATIONS FROM NEISSERIA-GONORRHOEAE.
AUTHOR(S): COOPER M D; TEWARI R P; BOWSER D V
CORPORATE SOURCE: DEP. MED. MICROBIOL. IMMUNOL., SOUTH. ILL. UNIV. SCH. MED., SPRINGFIELD, ILL. 63708, USA.
SOURCE: INFECT IMMUN, (1980) 28 (1), 92-100.
CODEN: INFIBR. ISSN: 0019-9567.
FILE SEGMENT: BA; OLD
LANGUAGE: English
TI IMMUNOGENICITY OF RIBOSOMAL PREPARATIONS FROM NEISSERIA-GONORRHOEAE.
SO INFECT IMMUN, (1980) 28 (1), 92-100.
CODEN: INFIBR. ISSN: 0019-9567.
AU COOPER M D; TEWARI R P; BOWSER D V
AB Protection against **gonococcal** infection was obtained by immunization with ribosomal preparations from N. gonorrhoeae. Ribosomes were isolated from disrupted cells by differential ultracentrifugation and **treatment** of the microsomal fraction with 0.25% sodium dodecyl sulfate. The isolated ribosomal preparations contained 55% RNA, 39% protein and 0.35% carbohydrate. The ribosomal preparations contained small amounts of endotoxin as determined by thiobarbituric acid- and lead acetate-sensitized mice assays. Guinea pigs immunized s.c. with ribosomal preparations were challenged intrachamberially with 107 colony-forming units of N. gonorrhoeae and protection was assessed by clearance of the organism from s.c. chambers. The ribosomal preparations elicited significant protection which was enhanced by incorporation of the **immunogen** into adjuvant. This protection was comparable to that obtained with whole cells. **Treatment** with proteolytic enzymes destroyed the protective effect of the ribosomal preparations, but RNase had no measurable effect. Passive hemagglutination and immunodiffusion tests with sera from immunized animals demonstrated the presence of antibody to the ribosomal antigens. Results of adsorption of anti-ribosomal sera with enzyme-treated ribosomal preparations indicated the protein nature of the **immunogen**. Protein associated with the **gonococcal** ribosomal preparation may be the major protective **immunogen**. The role of endotoxin contamination in the immunogenicity of **gonococcal** ribosomal preparations warrants further investigation.

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DNA vaccines. Mechanisms for generation of immune responses.
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Cell Mol Life Sci. 1999 May;55(5):751-70. Review.
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1: Gene Ther 1997 Mar;4(3):181-8

Immune-mediated destruction of transfected muscle fibers after direct gene transfer with antigen-expressing plasmid DNA.

Davis HL, Millan CL, Watkins SC.

Loeb Research Institute, Ottawa Civic Hospital, Canada.

DNA-based immunization of mice by intramuscular injection of antigen-encoding plasmid DNA results in immune responses which may be sustained for extended periods of time without an antigen boost. For example, we have previously shown that a strong humoral response against hepatitis B virus surface antigen (HBsAg) will persist for up to 74 weeks following a single intramuscular administration of DNA. It has been proposed that the longevity of the response is due to sustained expression of antigen in transfected muscle cells. However, here we show by immunohistochemistry and electron microscopy that HBsAg-expressing muscle fibers are destroyed around 10 days after injection of DNA in mice. We have also evaluated destruction of the transfected muscle fibers indirectly, by measurement of luciferase activity in muscles at different times after injection of a luciferase reporter gene construct, alone or in combination with HBsAg-expressing DNA. Control muscles injected with luciferase-expressing DNA alone maintain expression of high levels of luciferase for at least 60 days. In contrast, muscles co-injected with DNAs expressing luciferase and a secreted form of HBsAg show high levels of luciferase activity at 5 days but > 99% of this is lost by 20 days. Similar results are obtained with co-expression of luciferase and beta-galactosidase, a non-secreted antigen. Loss of luciferase expression does not occur in muscles of mice with severe combined immunodeficiency, indicating that the myofiber destruction is immunologically mediated.

PMID: 9135731 [PubMed - indexed for MEDLINE]

1: FEBS Lett 1997 Feb 3;402(2-3):107-10

Liposome-mediated DNA vaccination.

Gregoriadis G, Saffie R, de Souza JB.

The School of Pharmacy, University of London, UK. Gregoriadis@cua.ulsop.ac.uk

Numerous reports have indicated that intramuscular injection of antigen-coding naked plasmid DNA can trigger humoral and cell-mediated protective immunity against infection. This follows DNA uptake by muscle fibres, leading to the expression and extracellular release of the antigen. Here it is shown for the first time that intramuscular immunization of mice with pRc/CMV HBS (encoding the S region of hepatitis B antigen; HBsAg) entrapped into positively charged (cationic) liposomes leads to greatly improved humoral and cell-mediated immunity. These cationic liposome-entrapped DNA vaccines generate titres of anti-HBsAg IgG1 antibody isotype in excess of 100-fold higher and increased levels of both IFN-gamma and IL-4 when compared with naked DNA or DNA complexed with preformed similar (cationic) liposomes. It is likely that immunization with liposome-entrapped plasmid DNA involves antigen-presenting cells locally or in the regional draining lymph nodes.

PMID: 9037176 [PubMed - indexed for MEDLINE]

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mucosal and L4	52

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Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT; PLUR=YES; OP=OR			
L5	mucosal and L4	52	L5
L4	L1 and L2	326	L4
L3	L1 and L2L2	0	L3
L2	intramuscular adj injection	8233	L2
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR			
L1	papilloma adj virus	4115	L1

END OF SEARCH HISTORY

L5: Entry 11 of 52 File: USPT Mar 6, 2001

DOCUMENT-IDENTIFIER: US 6197755 B1
TITLE: Compositions and methods for delivery of genetic material

Brief Summary Paragraph Right (2):
The direct introduction of a normal, functional gene into a living animal has been studied as a means for replacing defective genetic information. In some studies, DNA is introduced directly into cells of a living animal without the use of a viral particle or other infectious vector. Nabel, E. G., et al., (1990) Science 249:1285-1288, disclose site-specific gene expression in vivo of a beta-galactosidase gene that was transferred directly into the arterial wall in mice. Wolfe, J. A. et al., (1990) Science 247:1465-1468, disclose expression of various reporter genes that were directly transferred into mouse muscle in vivo. Acsadi G., et al., (1991) Nature 352:815-818, disclose expression of human dystrophin gene in mice after intramuscular injection of DNA constructs. Wolfe, J. A., et al., 1991 BioTechniques 11 (4):474-485, which is incorporated herein by reference, refers to conditions affecting direct gene transfer into rodent muscle in vivo. Felgner, P. L. and G. Rhodes, (1991) Nature 349:351-352, disclose direct delivery of purified genes in vivo as drugs without the use of retroviruses.

Detailed Description Paragraph Right (65):
According to the invention, the gene constructs may be administered directly into the individual to be immunized or ex vivo into removed cells of the individual which are reimplanted after administration. By either route, the genetic material is introduced into cells which are present in the body of the individual. Routes of administration include, but are not limited to, intramuscular, intraperitoneal, intradermal, subcutaneous, intravenous, intraarterially, intraoccularly and oral as well as transdermally or by inhalation or suppository. Preferred routes of administration include intramuscular, intraperitoneal, intradermal and subcutaneous injection. Delivery of gene constructs which encode target proteins can confer mucosal immunity in individuals immunized by a mode of administration in which the material is presented in tissues associated with mucosal immunity. Thus, in some examples, the gene construct is delivered by administration in the buccal cavity within the mouth of an individual.

Detailed Description Paragraph Right (68):
The genetic vaccines and genetic therapeutics according to the present invention are formulated according to the mode of administration to be used. One having ordinary skill in the art can readily formulate a pharmaceutical composition that comprises a genetic construct. In cases where intramuscular injection is the chosen mode of administration, an isotonic formulation is preferably used. Generally, additives for isotonicity can include sodium chloride, dextrose, mannitol, sorbitol and lactose. In some cases, isotonic solutions such as phosphate buffered saline are preferred. Stabilizers include gelatin and albumin. In some embodiments, a vasoconstriction agent is added to the formulation. The pharmaceutical preparations according to the present invention are provided sterile and pyrogen free.

Detailed Description Paragraph Right (90):
Conjugated estrogenic hormones, is a natural product containing water-soluble, conjugated forms of mixed estrogens obtained from the urine of pregnant mares. It is water soluble and is commercially available in a formulation which may be reconstituted to a concentration of 25 mg/5 ml for intravenous or intramuscular injection; and in a vaginal cream containing 0.625 mg conjugated estrogens/gram (Premarin.RTM./Wyeth-Ayerst).

Detailed Description Paragraph Right (92):
The desired estrogenic compound(s) may conveniently be selected from a variety of products commercially available for human pharmaceutical use, preferably products in liquid parenteral formulation. To achieve mucosal immunity, e.g., immunity of the vaginal mucosa, a topical formulation such as an estrogen cream or jelly, may be used. Since facilitation of nucleic acid activity at the site of nucleic acid administration rather that systemic estrogenic or other hormonal activity is desired, a dose and concentration that achieves the desired local effect without significant systemic estrogenic or other hormonal activity will preferably be selected. Estrogen preparations may be formulated for parenteral administration as a genetic vaccine facilitating agent containing 0.001 mg/ml to 10 mg/ml estrogenic compound per ml, preferably 0.01 mg/ml to 1.0 mg/ml in a pharmaceutically acceptable carrier, preferably sterile water for injection, or sodium chloride injection, or another pharmaceutically acceptable aqueous injection fluid. Other doses and concentrations which achieve the desired facilitation of the effect of the genetic construct may be used. For this application an estrogenic compound is injected into the site of administration of the genetic construct, either before, after, and/or simultaneously, preferably simultaneously, with the administration of the genetic construct. Optimization of dose/concentration can be achieved using known methodology and routine experimentation by those of skill in pharmacology and the pharmaceutical sciences. A dose and concentration may be administered which provides the desired facilitation of uptake and/or enhancement of expression or immune response to the genetic constructs by cells. The desired estrogenic compound(s) may be administered before, after, and/or simultaneously, preferably simultaneously, with the desired nucleic acid construct.

Detailed Description Paragraph Right (100):
In some embodiments of the invention, the individual is first subject to GVF injection prior to genetic vaccination by intramuscular injection. That is, up to, for example, up to a about a week to ten days prior to vaccination, the individual is first injected with a GVF. In some embodiments, prior to vaccination, the individual is injected with a GVF about 1 to 5 days before administration of the genetic construct. In some embodiments, prior to vaccination, the individual is injected with a GVF about 24 hrs before administration of the genetic construct. Alternatively, a GVF can be injected simultaneously, minutes before or after vaccination. Accordingly, the GVF and the genetic construct may be combined and injected simultaneously as a mixture. In some embodiments, the GVF is administered after administration of the genetic construct. For example, up to about a week to ten days after administration of the genetic construct, the individual is injected with GVF. In some embodiments, the individual is injected with a GVF about 24 hrs after vaccination. In some embodiments, the individual is injected with a GVF about 1 to 5 days after vaccination. In some embodiments, the individual is administered a GVF up to about a week to ten days after vaccination.

Other Reference Publication (1):
Acsadi et al., "Human Dystrophin Expression in Mdx Mice After Intramuscular Injection of DNA Constructs", Nature, 1991, 352, 815-818.

CLAIMS:

12. The method of claim 10 wherein said pathogen is a virus selected from the group consisting of: human immunodeficiency virus, HIV; human T cell leukemia virus, HTLV; influenza virus; hepatitis A virus, HAV; hepatitis B virus, HBV; hepatitis C virus, HCV; human papilloma virus, HPV; Herpes simplex 1 virus, HSV1; Herpes simplex 2 virus, HSV2; Cytomegalovirus, CMV; Epstein-Barr virus, EBV; rhinovirus; and, coronavirus.

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L5: Entry 13 of 52 File: USPT Nov 21, 2000

DOCUMENT-IDENTIFIER: US 6149922 A
TITLE: Vaccine adjuvant and vaccine

Detailed Description Paragraph Right (16):
When used as an adjuvant, the polyoxyethylene/polyoxypropylene block copolymer of the present invention can be administered to a human or animal by a variety of routes including, but not limited to, intramuscular injection, intravenous injection, intraperitoneal injection, orally, rectal, vaginal, sublingually, and nasally.

Detailed Description Paragraph Right (21):
The composition of the present invention can be administered by a number of routes including, but not limited topical, transdermal, oral, trans-mucosal, subcutaneous injection, intravenous injection, intraperitoneal injection and intramuscular injection.

Detailed Description Paragraph Right (35):
Particulate vaccine antigens can also be delivered orally. Particulate antigens are more effectively `taken-up` by Peyer's patches and therefore are more efficient at inducing mucosal immune responses. The particulate property in itself appears to increase the ability of the immunogen to gain access to the Peyer's patches with the optimum size range being 1-10 .mu.m. Again, these are properties that are shared by the large, adjuvant active copolymers.

Detailed Description Paragraph Right (73):
The ability to deliver vaccine orally has two advantages over standard parenteral routes: (1) ease of administration and (2) the possibility of inducing mucosal immune responses. The large copolymers are well suited for use in vaccine formulations because (1) they are nonionic and therefore resistant to damage by stomach acids, (2) they inhibit lipase activity which should contribute to their utility with emulsions containing squalane, and (3) they can be used in aqueous formulations where they form appropriately sized particles.

Detailed Description Paragraph Type 1 (26):
Papilloma virus

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L5: Entry 15 of 52 File: USPT Sep 26, 2000

DOCUMENT-IDENTIFIER: US 6123948 A
TITLE: Polypeptides useful as immunotherapeutic agents and methods of polypeptide preparation

Brief Summary Paragraph Right (2):
Human papillomaviruses (HPV) are agents responsible for several benign and malignant lesions which proliferate in the skin and mucosal surfaces of humans. They are a genetically diverse group of DNA viruses which infect epithelial tissue, and can cause a range of different human diseases. Over 60 different types of HPV have been distinguished, based on the extent of cross hybridisation between their genomes, and of those, different subgroups are associated primarily with different types of disease. For example HPVs of types 1, 2, etc are associated with cutaneous warts of the hands and feet. HPVs 5 and 8 are associated with the rare disorder epidermodysplasia verruciformis.

Brief Summary Paragraph Right (10):
The use of HPV proteins such as L1, L2 in the preparation of vaccines is known for example from WO 93/02184 (Univ of Queensland & CLS Ltd: I Frazer et al: Papilloma virus vaccine). Other HPV proteins have been decribed for use in immunodiagnostics, e.g. in WO 91/18294 (Medscand AB: J Dillner et al: Synthetic peptides of various human papillomaviruses, for diagnostic immunossay); and EP 0 375 555 (Medgenix: G De Martynoff et al: Peptides, antibodies against them, and methods for detection and dosage of papilloma virus).

Brief Summary Paragraph Right (19):
The invention also provides fusion polypeptides that combine papilloma-virus-derived antigens, e.g. from each of at least two different papillomavirus proteins, e.g. comprising (a) at least an antigenic determinant of a papillomavirus L2 protein, and (b) at least an antigenic determinant selected from E1, E2, E4, E5, E6 and E7 papillomavirus proteins and L2 papillomavirus proteins of different papillomavirus type than in (a). Further fusion polypeptides provided hereby comprise antigenic determinants from at least two papillomavirus proteins selected from E1, E2, E4, E5, E6 and E7 papillomavirus proteins e.g. where the said proteins are from different papillomavirus types.

Detailed Description Paragraph Right (90):
A vaccine as described above, an aluminium hydroxide gel complex of L2E7 prepared equivalently as indicated above, has been shown to induce an appropriate dose-related immune response in healthy male volunteers. Cells from all of 36 vaccinated volunteers showed a L2E7-specific in-vitro lymphoproliferative response (CD4+T cells) indicative of immune response to the product. The volunteers had been given the product by intramuscular injection in doses of 3, 30 or 300 .mu.g, an initial dose at day 0 and repeated doses on day 7 and day 28 (accelerated schedule). (An alternative, slower, schedule for vaccination on days 0, 28 and 56 was also tried, and found less preferable.) Lymphoproliferative responses were seen from day 7 at dose levels including the lowest dose, 3 .mu.g. L2E7 specific antibody response was also shown in 29 of 32 assessable samples from the volunteers (the three non-responders in the antibody test had been given the lowest dose). Increased in-vitro production of IL-5, consistent with the antibody production, was also seen. The two higher doses elicited T-cell proliferation sooner than the lowest dose. The highest dose, 300 .mu.g, stimulated more IFN-gamma production than the lower doses. The observations made, of rapid T-cell proliferation and associated production of IFN-gamma, are appropriately consistent with the intended use of the product as a therapeutic vaccine for genital

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L5: Entry 17 of 52 File: USPT Jul 11, 2000

DOCUMENT-IDENTIFIER: US 6086899 A
TITLE: Vaccine adjuvant and vaccine

Detailed Description Paragraph Right (40):
Papilloma virus

Detailed Description Paragraph Right (135):
When used as an adjuvant, the polyoxyethylene/polyoxypropylene block copolymer of the present invention can be administered to a human or animal by a variety of routes including, but not limited to, intramuscular injection, intravenous injection, intraperitoneal injection, orally, rectal, vaginal, sublingually, and nasally.

Detailed Description Paragraph Right (143):
The composition of the present invention can be administered by a number of routes including, but not limited topical, transdermal, oral, trans-mucosal, subcutaneous injection, intravenous injection, intraperitoneal injection and intramuscular injection.

Detailed Description Paragraph Right (158):
Particulate vaccine antigens can also be delivered orally. Particulate antigens are more effectively `taken-up` by Peyer's patches and therefore are more efficient at inducing mucosal immune responses. The particulate property in itself appears to increase the ability of the immunogen to gain access to the Peyer's patches with the optimum size range being 1-10 .mu.m. Again, these are properties that are shared by the large, adjuvant active copolymers.

Detailed Description Paragraph Right (197):
The ability to deliver vaccine orally has two advantages over standard parenteral routes: (1) ease of administration and (2) the possibility of inducing mucosal immune responses. The large copolymers are well suited for use in vaccine formulations because (1) they are nonionic and therefore resistant to damage by stomach acids, (2) they inhibit lipase activity which should contribute to their utility with emulsions containing squalane, and (3) they can be used in aqueous formulations where they form appropriately sized particles.

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L5: Entry 9 of 52 File: USPT Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6218166 B1
TITLE: Adjuvant incorporation into antigen carrying cells: compositions and methods

Detailed Description Paragraph Right (175):
The preparation of more, or highly, concentrated solutions for intramuscular injection is also possible. In this regard, the use of DMSO as solvent is preferred as this will result in extremely rapid penetration, delivering high concentrations of the cells to a small area.

Detailed Description Paragraph Type 0 (60):
Garg & Subbarao, "Immune Responses of Systemic and Mucosal Lymphoid Organs to Pnu-Immune Vaccine as a Function of Age and the Efficacy of Monophosphoryl Lipid A as an Adjuvant," Infection and Immunity, 60(6):2329-2336, 1992.

Detailed Description Paragraph Table (1):
TABLE 1 Exemplary Adjuvants for Conjugation to Cells. Alhydrogel Alkyl lysophosphilipids (ALP) BCG Bestatin Biliverdin including derivatives and glycoconjugates Bilirubin including derivatives and glycoconjugates, such as monoglycouranoglycans and diglycouranoglycans Biotin including biotinylated derivatives Carnosine including derivatives Chitin Citosan deacetylated chitin Cholesteryl succinate Cornyebacteriuin parvum whole or part of cell including oligosaccharides and glycolipids C. granulosum whole or part of cell including P40 a peptidoglycan with a glycoprotein monophoshoryl lipid A deacetylated monophosphoryl lipid A synthetic isoprinosine lithosperman lithosperman A, lithosperman B or lithosperman C Trehalose monomycolate Trehalose dimycolate Mycobacterial species whole or part of cell including glycolipids, phenolic glycolipids, peptides such as 45/47 kda and BCG Muramyl dipeptide N-acetyl muramyl-L-alanyl-D-isoglutamine Muramyl tripeptide MF75.2 threonyl-muramyl dipeptide murametide murabutide lipoteichoic acid LTA ribitol teichoic acid RTA glycerol teichoic acid GTA Superantigens S. aureus enterotoxins S. epidermidis enterotoxins S. pyogenes enterotoxins E. coli exotoxins Staphylococcus species whole or part of cell including peptidoglycans and enterotoxins Viruses whole or part of particle including Vaccinia, Newcastle disease visurs, vesicular stomatitis virus, papilloma virus and rhinovirus synthetic peptides pentamers, hexamers, heptamers, octamers, nonamers, decamers, etc.; such as polylysine and threonine- alanine peptides Recombinant Prolactin Glycosaminoglycans and lipid and peptide derivatives glycosaminoglycouranoglycans glycosaminoglycolipids glycosaminoglycouranoglycolipids glycosaminoglycopeptides glycosaminoglycouranoglycopeptides phosphorylated glycosaminoglycans sulphanted glycosaminoglycan QS-21 Quil-A Polymethylmethyl acrylate (PMMA) Retinoic acid Lentinan Levan Malic anhydride-divinyl ether (MVE-2) hemocyanin from keyhole limpet (KLH) hemoerythrin molluscan, arthropod hemoerythrin from annelids and lower invertebrates pteridines nucleic acids preferably poly A, poly T, poly AT, poly GC and poly IC-LC oligonucleotides varying kilobases lentinen lectins part or whole; from plants and animals

Other Reference Publication (42):
Garg & Subbarao, "Immune Response of Systemic and Mucosal Lymphoid Organs to Pnu-Immune Vaccine as a Function of Age and the Efficacy of Monophosphoryl Lipid A as an Adjuvant," Infection and Immunity, 60(6):2329-2336, 1992.

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L17: Entry 29 of 51 File: USPT Feb 16, 1999

DOCUMENT-IDENTIFIER: US 5872104 A
TITLE: Combinations and methods for reducing antimicrobial resistance

Brief Summary Paragraph Right (15):
The microorganism, e.g., bacterium, or population thereof, may be contacted either in vitro or in vivo. Contacting in vivo may be achieved by administering to an animal (including a human patient) that has, or is suspected to have a microbial or bacterial infection, a therapeutically effective amount of pharmacologically acceptable antimicrobial agent formulation in combination with a therapeutic amount of a pharmacologically acceptable formulation of a second agent effective to inhibit methylation, e.g., effective to inhibit RNA methylation. The invention may thus be employed to treat both systemic and localized microbial and bacterial infections by introducing the combination of agents into the general circulation or by applying the combination, e.g., topically to a specific site, such as a wound or burn, or to the eye, ear or other site of infection.

Brief Summary Paragraph Right (20):
The ID.sub.50 /IC.sub.50 ratio required for safe use of the proposed inhibitor-antimicrobial agent combinations will be assessed by determining the ID.sub.50 (median lethal toxic dosage) and the IC.sub.50 (median effective therapeutic dosage) in experimental animals. The optimal dose for human subjects is then defined by fine-tuning the range in clinical trials. In the case of ID.sub.50, the inhibitor is usually administered to mice or rats (orally or intraperitoneal) at several doses (usually 4-5) in the lethal rage. The dose in mg/kg is plotted against % mortality and the dose at 50% represents the ID.sub.50 (Klaassen, 1990). The IC.sub.50 is determined in a similar fashion as described by Cleeland & Squires (1991).

Brief Summary Paragraph Right (45):
In the treatment of animals or human patients, there are various appropriate formulations and treatment regimens that may be used. For example, the antimicrobial compound(s) and second agent(s) may be administered to an animal simultaneously, e.g., in the form of a single composition that includes the microbial/antibiotic and second agent, or by using at least two distinct compositions. The antimicrobial agent could also be administered to the animal prior to the second agent, although it is currently more preferred to give the second agent inhibitor prior to the antimicrobial agent.

Detailed Description Paragraph Right (67):
In vitro tests are useful as the starting point in the development of new drugs and combinations for use in treatment. However, no such drug or combination of agents should then be administered to a human patient solely on the basis of in vitro activity. This invention provides inhibitory compounds for use in combination with antimicrobials, which compounds have been selected on the basis of reported functional characteristics. As no such inhibitory compound is selected randomly, it is expected that the correlation between in vitro and in vivo data will be high.

Detailed Description Paragraph Right (79):
In developing an experimental mouse model for in vivo testing, it is desirable to use human pathogens whenever possible. It is also desirable to infect with strains of microorganisms that are sufficiently virulent so that conditioning procedures to lower the host's resistance are unnecessary. When reproducible infections cannot be achieved by inoculation of the organisms alone, adjuvant stressing measures can be used to lower the host's resistance. In the case of injections with Staphylococcus aureus, a commonly employed measure is to suspend the organisms in 3 to 10% hog gastric mucin

and to administer 0.5 ml amounts by the intraperitoneal route.

Detailed Description Paragraph Right (82):
The mouse protection test has been studied in great detail, and evaluation of antibacterials using this method has produced a number of clinically effective agents (Grunberg & Cleeland, 1977). Various studies have shown that using the mouse protection test the PD.sub.50 values generally fall into the same ranges as the clinical doses measured in mg/kg. However, this is not an indication that the doses in the mouse models should be exactly the doses employed in the clinical management of infections. Certainly humans are not treated on the basis of achieving only 50% survival. In spite of this, there is a reasonable overall correlation between the results obtained in the mouse model and clinical effectiveness.

Detailed Description Paragraph Right (84):
In the mouse protection tests described above, the infections are primarily of short duration, unnatural and overwhelming or self-limiting. A number of specific infections in a variety of animal hosts have been utilized to mimic human infections more precisely and will be known to those of skill in the art. Examples that appear to be reasonably faithful to the human infection are pyelonephritis in the rat and meningitis, endocarditis and osteomyelitis in the rabbit. In a number of other experimental infections, the targeting of infection to specific organs, while not as close in mimicking the human situation (e.g., meningitis and pneumonia in mice), provide useful models for predicting the selectivity of new agents and combinations.

Detailed Description Paragraph Right (87):
The thigh lesion model provides a nonlethal experimental infection to evaluate the effectiveness of an antimicrobial combination and allows the measurement of drug-pathogen interaction and drug pharmacokinetics in the infected host. If the animals are made neutropenic, then the thigh model becomes an excellent system for measuring the drug-microorganism interaction with most of the host defense system eliminated (Vogelman et al., 1988).

Detailed Description Paragraph Right (88):
Regarding respiratory tract infections, such as pneumonia, various models are available. For example, in the mouse model of pneumonia, disease is induced in mice by intranasal instillation of 3 drops of an undiluted overnight culture of Streptococcus pneumoniae 6301 in trypticase soy broth containing 5% goat serum (Beskid et al., 1981). A useful model for the production of pneumococcal pneumonia in rats has been described by Ansfield et al. (1977). For the detection of antitubercular drugs, a number of mice systems have been described. An infection in guinea pigs useful for testing new antitubercular agents is also available. In this model. M. tuberculosis H37Rv, whether inoculated by the subcutaneous or intramuscular routes, produces a progressive, predictable disease.

Detailed Description Paragraph Right (93):
Models are even available for sexually transmitted diseases. Corbeil et al. (1979) have described a mouse model for disseminated gonococcal infections, using a gonococcal strain (N24) isolated from a human genital tract. The most successful model for studying gonococcal urethritis is produced by the inoculation of chimpanzees with human urethral exudate (Arka & Balows, 1986). Johnson et al. (1982) have described a method for experimentally inducing syphilis in rabbits.

Detailed Description Paragraph Right (113):
Gillet et al. (1979) also described a number of SAH analogues mainly modified in the amino acid portion of the molecule, that are all effective competitive inhibitors of protein methyltransferase II from human erythrocytes. From these analogues, the inventors propose that 5'-S-(3-carboxyl-4-nitrophenyl)thioadenosine, S-adenosyl-L-homocysteine sulfoxide and 5'-S-(methyl)-5'-S-(butyl)thioadenosine would be particularly useful in connection with this invention.

Detailed Description Paragraph Right (121):
Polyinosinate with molecular mass ranging from 5000-200,000 is preferred for use in the present invention. From the data of Liau et al. (1973) and Levy & Merrigan (1977), the inventors contemplate that concentrations of poly(I) useful in therapy with agents such as MLS antibiotics, will be from about 0.1 mg/kg/day to about 30 mg/kg/day, and

preferably, from about 0.1 to about 10 mg/kg/day. Poly(I) has been proposed for use in cancer chemotherapy and is thus considered suitable for human administration. Polyinosinate is commercially available from P-L Biochemicals (Milwaukee, Wis.).

Detailed Description Paragraph Right (158):
Kitaoka et al. (1986) studied several nucleoside analogues known to have broad spectrum antiviral activity, e.g., ribavirin, vidarabine (Ara A), pyraazofurin, tubercidin, carbodine, [(S)-DHPA], (C-c.sup.3 Ado), [(RS)-AHPA] isobutyl ester and neplanocin A. These compared for their potency and selectivity as inhibitors of human retrovirus replication in vitro. These adenosine analogues were proposed to also owe their antiviral activity to the inhibition of SAH hydrolase. The studies of Kitaoka et al. (1986), reported effective inhibitory concentrations of (S)-DPHA, C-C.sup.3 Ado, (RS)-AHPA isobutyl ester and NPA are about 60, 1.4, 1.2 and 0.2 .mu.g/ml, respectively. In vitro cytotoxicity indicated an activity index of >3, 70. 80 and >20 respectively for (S)-DPHA), C-C.sup.3 Ado, (RS)-AHPA isobutyl ester and NPA, suggesting a potential for in vivo use.

Detailed Description Paragraph Right (163):
2'-deoxy-2'-chloroadenosine (CLA) was shown to be an inhibitor of hamster and human liver SAHH (Kim et al., 1985). Buckle et al. (1981) evaluated CLA at dosages of 300 .mu.Mol/kg (90 mg/kg) in mice. Based on these observations, it is proposed that CLA in combination with, e.g., MLS antibiotics, will provide enhanced killing at dosages between 1 and 150 mg/kg/day, and preferably, at between 10-90 mg/kg/day.

Detailed Description Paragraph Right (170):
Glazer & Knode (1984) also studied the activity of NPA against human colon carcinoma in vitro. They determined NPA to be an inhibitor of RNA methylation, but not of RNA synthesis (transcription). These properties confer to NPA unique pharmacological characteristics not possessed by other adenosine analogues studied at that time. Consequently, NPA should be a valuable tool for further chemotherapeutic studies.

Detailed Description Paragraph Right (179):
2'-Deoxyadenosine and 9-B-arabinofuranosyladenine (Ara-A) are suicide inactivators of SAH hydrolase (Hershfield, 1979; Helland & Ueland, 1982). Ara-A appears to be twice as active as 2'-deoxyadenosine. Ara-A is approved by the FDA for use as an ophthalmic ointment for herpes simplex virus infections and also as a systemic treatment for herpes simplex encephalitis at a dosage of 15 mg/kg/day for 10 days (Berkow et al., 1992). This suggested to the inventors that Ara-A could be used therapeutically.

Detailed Description Paragraph Right (263):
The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce adverse, allergic or other untoward reactions when administered to an animal, or a human, as appropriate. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, additional antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like (USP XXII, The United States Pharmacopeia, 1990; incorporated herein by reference).

Detailed Description Paragraph Right (267):
The active compounds, whether antibiotics, second agent inhibitors, or combinations thereof, may be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes (USP XXII, The United States Pharmacopeia, 1990). The preparation of an aqueous composition that contains such active ingredients, or combinations thereof, will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared, and the preparations can also be emulsified.

Detailed Description Paragraph Right (273):
The preparation of more, or highly, concentrated solutions for intramuscular injection is also contemplated. This is envisioned to have particular utility in cases where either the antibiotic or the inhibitor is sensitive to digestive conditions. In this regard, the use of DMSO as solvent is preferred as this will result in extremely rapid

penetration, delivering high concentrations of the active agents to a small area.

Detailed Description Paragraph Right (274):
Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as are therapeutically effective, as outlined in the foregoing examples. The formulations are easily administered in a variety of dosage forms. For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1033 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

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L12	human and L11	276	L12
L11	L10	281	L11
L10	L9	281	L10
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L8	Herpesvirus and composition	2055	L8
L7	intramuscular adj injection and L6	55	L7
L6	HIV and L4	413	L6
L5	HIV and L4L4	0	L5
L4	Immunogenic adj composition	1485	L4
L3	Intramuscular and L2	4	L3
L2	HIV and L1	4	L2
L1	" Immune composition"	27	L1

END OF SEARCH HISTORY

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L7: Entry 28 of 55 File: USPT Mar 7, 2000

US-PAT-NO: 6034298
DOCUMENT-IDENTIFIER: US 6034298 A

TITLE: Vaccines expressed in plants

DATE-ISSUED: March 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Prodigene, Inc.	College Station	TX			02

APPL-NO: 8/ 481291 [PALM]
DATE FILED: August 23, 1996

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This is a U.S. National Phase application of PCT/US94/02332 filed Mar. 4, 1994 which is a continuation-in-part of U.S. Pat. No. 08/026,393, filed Mar. 4, 1993, now U.S. Pat. No. 5,612,487, issued Mar. 18, 1997, which is a continuation-in-part of U.S. Pat. No. 07/750,049, filed Aug. 26, 1991, now abandoned.

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/US94/02332	March 4, 1994	WO94/20135	Sep 15, 1994	Aug 23, 1996	Aug 23, 1996

INT-CL: [7] A01 H 1/04, A61 K 39/12, A61 K 39/225, C12 N 15/00

US-CL-ISSUED: 800/298; 800/288, 800/317.2, 435/320.1, 424/186.1, 424/223.1, 424/195.1
US-CL-CURRENT: 800/298; 424/186.1, 424/223.1, 424/725, 435/320.1, 800/288, 800/317.2

FIELD-OF-SEARCH: 435/69.1, 435/172.1, 435/172.3, 435/320.1, 435/375, 435/410, 435/411, 435/417, 800/205, 800/250, 800/255, 800/DIG.44, 800/DIG.42, 800/288, 800/298, 800/317.2, 536/23.72, 536/24.1, 424/186.1, 424/223.1, 424/195.1

PRIOR-ART-DISCLOSED:

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☐	5612487	March 1997	Lam et al.	800/205
☐	5654184	August 1997	Curtiss, III et al.	435/172.3

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ART-UNIT: 162
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ABSTRACT:

The anti-viral vaccine of the present invention is produced in transgenic plants and then administered through standard vaccine introduction method or through the consumption of the edible portion of those plants. A DNA sequence encoding for the expression of a surface antigen of a viral pathogen is isolated and ligated to a promoter which can regulate the production of the surface antigen in a transgenic plant. This gene is then transferred to plant cells using a procedure that results in its integration into the plant genome, such as through the use of an Agrobacterium tumefaciens plasmid vector system. Preferably, the foreign gene is expressed in a portion of the plant that is edible by humans or animals. In a preferred procedure, the vaccine is administered through the consumption of the edible plant as food, preferably in the form of a fruit or vegetable juice which can be taken orally.

12 Claims, 11 Drawing figures

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L7: Entry 26 of 55 File: USPT May 16, 2000

US-PAT-NO: 6063384
DOCUMENT-IDENTIFIER: US 6063384 A

TITLE: Encapsidated recombinant viral nucleic acid and methods of making and using same

DATE-ISSUED: May 16, 2000

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/199.1; 424/208.1, 424/217.1, 435/320.1, 435/69.3

CLAIMS:

What is claimed is:

1. A method for stimulating an immune response to an immunogenic protein or fragment thereof, in a subject, comprising

administering, in a physiologically acceptable carrier, an effective amount of a composition comprising a recombinant poliovirus nucleic acid having a foreign nucleotide sequence encoding, in an expressible form, an immunogenic protein or fragment thereof substituted for the entire P1 capsid precursor region of the poliovirus genome.

2. The method of claim 1 wherein the recombinant poliovirus nucleic acid is encapsidated.

3. The method of claim 1 wherein the composition is administered orally or by intramuscular injections.

4. The method of claim 1 wherein the immunogenic protein or fragment thereof is a human immunodeficiency virus type 1 protein or fragment thereof.

5. The method of claim 4 wherein the human immunodeficiency virus type 1 protein or fragment thereof is selected from the group consisting of the gag protein, the pol protein, and the env protein of human immunodeficiency virus type 1.

6. The method of claim 5 wherein the human immunodeficiency virus type 1 protein or fragment thereof comprises the human immunodeficiency virus type 1 gag protein (SEQ ID NO: 17).

7. The method of claim 1 wherein the immunogenic protein or fragment thereof is a tumor-associated antigen or fragment thereof.

8. The method of claim 7 wherein the tumor-associated antigen is carcinoembryonic antigen.

9. A method for stimulating in a subject an immune response to the gag protein of the

human immunodeficiency virus type 1, comprising

administering, in a physiologically acceptable carrier, an effective amount of a composition comprising an encapsidated recombinant poliovirus nucleic acid having the nucleotide sequence of the human immunodeficiency virus type 1 gag gene, in expressible form, substituted for the entire P1 capsid precursor region of the poliovirus genome.

10. A method for stimulating in a subject an immune response to carcinoembryonic antigen, comprising

administering, in a physiologically acceptable carrier, an effective amount of a composition comprising an encapsidated recombinant poliovirus nucleic acid having the nucleotide sequence of the gene encoding the carcinoembryonic antigen, in expressible form, substituted for the entire P1 capsid precursor region of the poliovirus genome.

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L3: Entry 1 of 4 File: USPT Oct 24, 2000

DOCUMENT-IDENTIFIER: US 6136320 A
TITLE: Vaccines expressed in plants

Brief Summary Paragraph Right (18):
such oral administration requires relatively large quantities of antigen since the amount of the antigen that is actually absorbed and capable of eliciting an immune response is usually low. Thus, the amount of antigen required for oral administration generally far exceeds that required for parenteral administration. de Aizpurua and Russell-Jones, J. Exp. Med. 167:440-451 (1988). However, it has been found that the systemic and mucosal immune systems may be stimulated by feeding low doses of certain classes of proteins. In particular, this may be achieved with proteins which share the property of being able to bind specifically to various glycolipids and glycoproteins located on the surface of the cells on the mucosal membrane. Such proteins, called "mucosal immunogens" have been found to include viral antigens such as viral hemagglutinin. Moreover, dose-response experiments comparing oral with intramuscular administration revealed that oral presentation of mucosal immunogens was remarkably efficient in eliciting a serum antibody response to the extent that the response elicited by oral presentation was only slightly lower than that elicited by intramuscular injection of the mucosal immunogen. de Aizpurua and Russell-Jones, supra.

Detailed Description Paragraph Right (10):
While the vaccines of the present invention will be preferably utilized directly as oral vaccines of the transgenic plant material, immunogenic compositions derived from the transgenic plant materials suitable for use as more traditional immune vaccines may be readily prepared from the transgenic plant materials described herein. Preferably, such immune compositions will comprise a material purified from the transgenic plant. Purification of the antigen may take many forms known well to those of skill in the art, in particular such purifications will likely track closely the purification techniques used successfully in obtaining viral antigen particles from recombinant yeasts (i.e., those containing HBsAg). In one embodiment, detailed in the examples to follow, HBsAg viral protein-containing particles, similar in many respects to those obtained from recombinant yeasts, were purified from transformed tobacco plants using a particular purification procedure. Whatever initial purification scheme is utilized, the purified material will also be extensively dialyzed to remove undesired small molecular weight molecules (i.e., sugars, pyrogens) and/or lyophilization of the thus purified material for more ready formulation into a desired vehicle.

Other Reference Publication (26):
Forrest, B.D., "Women, HIV, and Mucosal Immunity", The Lacet, vol. 337, pp. 835-836 (1991).

L14: Entry 7 of 118 File: USPT Jan 15, 2002

DOCUMENT-IDENTIFIER: US 6339068 B1
TITLE: Vectors and methods for immunization or therapeutic protocols

Drawing Description Paragraph Right (6):
FIG. 6: Synthetic ODN cannot be mixed with DNA vaccine due to interference with expression from plasmid. The figure shows the effect of adding S-ODN to plasmid DNA expressing reporter gene or antigen. ODN 1826 (10 or 100 .mu.g) was added to DNA constructs (10 .mu.g) encoding hepatitis B surface antigen (HBsAg) (pCMV-S, top panel) or luciferase (pCMV-luc, bottom panel) DNA prior to intramuscular (IM) injection into mice. There was an ODN dose-dependent reduction in the induction of antibodies against HBsAg (anti-HBs, end-point dilution titers at 4 wk) by the pCMV-S DNA (top panel) and in the amount of luciferase expressed in relative light units per sec per mg protein (RLU/sec/mg protein at 3 days) from the pCMV-luc DNA (bottom panel). This suggests that the lower humoral response with DNA vaccine plus ODN was due to decreased antigen expression. Each bar represents the mean of values derived from 10 animals (top panel) or 10 muscles (bottom panel) ands vertical lines represent the SEM. Numbers below the bars indicate proportion of animals responding to the DNA vaccine (top panel); all muscles injected with pCMV-luc expressed luciferase (bottom panel).

Detailed Description Paragraph Right (2):
DNA vaccines have been found to induce potent humoral and cell-mediated immune responses. These are frequently Th1-like, especially when the DNA is administered by intramuscular injection (Davis, H. L. (1998) Gene-based Vaccines. In: Advanced Gene Delivery: From Concepts to Pharmaceutical Products (Ed. A. Rolland), Harwood Academic Publishers (in press); Donnelly et al., Life Sciences 60:163, 1997; Donnelly et al., Ann Rev. Immunol. 15:617, 1997; Sato et al., Science 273:352, 1996). Most DNA vaccines comprise antigen-expressing plasmid DNA vectors. Since such plasmids are produced in bacteria and then purified, they usually contain several unmethylated immunostimulatory CpG-S motifs. There is now convincing evidence that the presence of such motifs is essential for the induction of immune responses with DNA vaccines (see Krieg et al., Trends Microbiology. 6: 23-27, 1998). For example, it has been shown that removal or methylation of potent CpG-S sequences from plasmid DNA vectors reduced or abolished the in vitro production of Th1 cytokines (e.g., IL-12, IFN-.alpha., IFN-.gamma.) from monocytes and the in vivo antibody and CTL response against an encoded antigen (.beta.-galactosidase) (Sato et al., 1996, supra; Klimnan et al., J. Immunol 158: 3635-3639 (1997). Potent responses could be restored by cloning CpG-S motifs back into the vectors (Sato et al., 1996, supra) or by coadministering CpG-S ODN (Klinan et al., 1997, supra). The humoral response in monkeys to a DNA vaccine can also be augmented by the addition of E. coli DNA (Gramzinski et al., Molec. Med. 4: 109-119, 1998). It has also been shown that the strong Th1 cytokine pattern induced by DNA vaccines can be obtained with a protein vaccine by the coadministration of empty plasmid vectors (Leclerc et al., Cell Immunology. 170: 97-106, 1997).

Detailed Description Paragraph Right (8):
The choice of motifs also depends on the species to be immunized as different motifs are optimal in different species. Thus, there would be one set of cassettes for humans as well as cassettes for different companion and food-source animals which receive veterinary vaccination. There is a very strong correlation between certain in vitro immunostimulatory effects and in vivo adjuvant effect of specific CpG motifs. For example, the strength of the humoral response correlates very well (r>0.9) with the in vitro induction of TNF-.alpha., IL-6, IL-12 and B-cell proliferation. On the other hand, the strength of the cytotoxic T-cell response correlates well with in vitro induction of IFN-.gamma..

Detailed Description Paragraph Right (9):
Since the entire purpose of DNA vaccines is to enhance immune responses, which necessarily includes cytokines, the preferred promoter is not down-regulated by cytokines. For example, the CMV immediate-early promoter/enhancer, which is used in almost all DNA vaccines today, is turned off by IFN-.alpha. and IFN-.gamma. (Gribaudo et al., Virology. 197: 303-311, 1993; Harms & Splitter, Human Gene Ther. 6: 1291-1297, 1995; Xiang et al., Vaccine, 15: 896-898, 1997). Another example is the down-regulation of a hepatitis B viral promoter in the liver of HBsAg-expressing transgenic mice by IFN-.gamma. and TNF-.alpha. (Guidotti et al., Proc. Natl. Acad. Sci. USA. 91: 3764-3768, 1994).

Detailed Description Paragraph Right (10):
Nevertheless, such viral promoters may still be used for DNA vaccines as they are very strong, they work in several cell types, and despite the possibility of promoter turn-off, the duration of expression with these promoters has been shown to be sufficient for use in DNA vaccines (Davis et al., Human Molec. Genetics. 2: 1847-1851, 1993). The use of CpG-optimized DNA vaccine vectors could improve immune responses to antigen expressed for a limited duration, as with these viral promoters. When a strong viral promoter is desired, down-regulation of expression may be avoidable by choosing CpG-S motfis that do not induce the cytokine(s) that affect the promoter (Harms and Splitter, 1995 supra).

Detailed Description Paragraph Right (13):
After intramuscular injection of DNA vaccines, muscle fibers may be efficiently transfected and produce a relatively large amount of antigen that may be secreted or otherwise released (e.g., by cytolytic attack on the antigen-expressing muscle fibers) (D)avis et al., Current Opinions Biotech. 8: 635-640, 1997). Even though antigen-expressing muscle fibers do not appear to induce immune responses from the point of view of antigen presentation, B-cells must meet circulating antigen to be activated, it is possible that antibody responses are augmented by antigen secreted or otherwise released from other cell types (e.g., myofibers, keratinocytes). This may be particularly true for conformational B-cell epitopes, which would not be conserved by peptides presented on APC. For this purpose, expression in muscle tissue is particularly desirable since myofibers are post-mitotic and the vector will not be lost through cell-division, thus antigen expression can continue until the antigen-expressing cell is destroyed by an immune repsonse against it. Thus, when strong humoral responses are desired, other preferred promoters are strong muscle-specific promoters such as the human muscle-specific creatine kinase promoter (Bartlett et al., 1996) and the rabbit .beta.-cardiac myosin heavy chain (full-length or truncated to 781 bp) plus the rat myosin light chain 1/3 enhancer.

Detailed Description Paragraph Right (25):
DNA vaccines will preferably be administered by direct (in vivo) gene transfer. Naked DNA can be give by intramuscular (Davis et al., 1993), intradermal (Raz et al., 1994; Condon et al., 1996; Gramzinski et al., 1998), subcutaneous, intravenous (Yokoyama et al., 1996; Liu et al., 1997), intraaterial (Nabel et al., 1993) or buccal injection (Etchart et al., 1997; Hinkula et al., 1997). Plasmid DNA may be coated onto gold particles and introduced biolistically with a "gene-gun" into the epidermis if the skin or the oral or vaginal mucosae (Fynan et al Proc. Natl. Acad. Sci. USA 90:11478, 1993; Tang et al, Nature 356:152, 1992; Fuller, et al, J. Med. Primatol. 25:236, 1996; Keller et al., Cancer Gene Ther., 3:186, 1996). DNA vaccine vectors may also be used in conjunction with various delivery systems. Liposomes have been used to deliver DNA vaccines by intramuscular injection (Gregoriadis et al, FEBS Lett.402:107, 1997) or into the respiratory system by non-invasive means such as intranasal inhalation (Fynan et al., supra). Other potential delivery systems include microencapsulation (Jones et al., 1998; Mathiowitz et al., 1997) or cochleates (Mannino et al., 1995, Lipid matrix-based vaccines for mucosal and systemic immunization. Vaccine Designs: The Subunit and Adjuvant Approach, M. F. Powell and M. J. Newman, eds., Pleum Press, New York, 363-387), which can be used for parenteral, intranasal (e.g., nasal spray) or oral (e.g., liquid, gelatin capsule, solid in food) delivery. DNA vaccines can also be injected directly into tumors or directly into lymphoid tissues (e.g., Peyer's patches in the gut wall). It is also possible to formulate the vector to target delivery to certain cell types, for example to APC. Targeting to APC such as dendritic cells is possible through attachment of a mannose moiety (dendritic cells have a high density

of mannose receptors) or a ligand for one of the other receptors found preferentially on APC. There is no limitation as to the route that the DNA vaccine is delivered, nor the manner in which it is formulated as long as the cells that are transfected can express antigen in such a way that an immune response is induced.

Detailed Description Paragraph Right (29):
It is envisioned that methods of the present invention can be used to prevent or treat bacterial, viral, parasitic or other disease states, including tumors, in a subject. The subject can be a human or may be a non-human such as a pig, cow, sheep, horse, dog, cat, fish, chicken, for example. Generally, the terms "treating," "treatment," and the like are used herein to mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a particular infection or disease (e.g. bacterial, viral or parasitic disease or cancer) or sign or symptom thereof, and/or may be therapeutic in terms of a partial or complete cure for an infection or disease and/or adverse effect attributable to the infection or disease. "Treating" as used herein covers any treatment of (e.g. complete or partial), or prevention of, an infection or disease in a non-human, such as a mammal, or more particularly a human, and includes:

Detailed Description Paragraph Right (30):
The pharmaceutical compositions are preferably prepared and administered in dose units. Liquid dose units would be injectable solutions or nasal sprays or liquids to be instilled (e.g., into the vagina) or swallowed or applied onto the skin (e.g., with allergy tines, with tattoo needles or with a dermal patch). Solid dose units would be DNA-coated gold particles, creams applied to the skin or formulations incorporated into food or capsules or embedded under the skin or mucosae or pressed into the skin (e.g., with allergy tines). Different doses will be required depending on the activity of the compound, form and formulation, manner of administration, and age or size of patient (i.e., pediatric versus adult), purpose (prophylactic vs therapeutic). Doses will be given at appropriate intervals, separated by weeks or months, depending on the application. Under certain circumstances higher or lower, or more frequent or less frequent doses may be appropriate. The administration of a dose at a single time point may be carried out as a single administration or a multiple administration (e.g., several sites with gene-gun or for intradermal injection or different routes). Whether the pharmaceutical composition is delivered locally or systemically, it will induce systemic immune responses. By "therapeutically effective dose" is meant the quantity of a vector or construct according to the invention necessary to induce an immune response that can prevent, cure, or at least partially arrest the symptoms of the disease and its complications. Amounts effective for this will of course depend on the mode of administration, the age of the patient (pediatric versus adult) and the disease state of the patient. Animal models may be used to determine effective doses for the induction of particular immune responses and in some cases for the prevention or treatment of particular diseases.

Detailed Description Paragraph Right (32):
In one embodiment, the invention provides a nucleic acid construct containing CpG motifs as described herein as a pharmaceutical composition useful for inducing an immune response to a bacterial, parasitic, fingal, viral infection, or the like, or to a tumor in a subject, comprising an immunologically effective amount of nucleic acid construct of the invention in a pharmaceutically acceptable carrier. "Administering" the pharmaceutical composition of the present invention may be accomplished by any means known to the skilled artisan. By "subject" is meant any aninal, preferably a mammal, most preferably a human. The term "immunogenically effective amount," as used in describing the invention, is meant to denote that amount of nucleic acid construct which is necessary to induce, in an animal, the production of a protective immune response to the bacteria, fungus, virus, tumor, or antigen in general.

Detailed Description Paragraph Right (33):
In addition to the diluent or carrier, such compositions can include adjuvants or additional nucleic acid constructs that express adjuvants such as cytokines or co-stimulatory molecules. Adjuvants include CpG motifs such as those described in co-pending application Ser. No. 09/030,701.

Detailed Description Paragraph Right (35):
Many different techniques exist for the timing of the immunizations when a multiple

immunization regimen is utilized. It is possible to use the antigenic preparation of the invention more than once to increase the levels and diversity of expression of the immune response of the immunized animal. Typically, if multiple immunizations are given, they will be spaced about four or more weeks apart. As discussed, subjects in which an immune response to a pathogen or cancer is desirable include humans, dogs, cattle, horses, deer, nice, goats, pigs, chickens, fish, and sheep.

Detailed Description Paragraph Right (36):
Examples of infectious virus to which stimulation of a protective immune response is desirable include: Retroviridae (e.g., human immunodeficiency viruses, such as HIV-1 (also referred to as HTLV-III, LAV or HTLV-III/LAV, or HIV-III; and other isolates, such as HIV-LP; Picornaviridae (e.g., polio viruses, hepatitis A virus; enteroviruses, human coxsackie viruses, rhinoviruses, echoviruses); Calciviridae (e.g., strains that cause gastroenteritis); Togaviridae (e.g., equine encephalitis viruses, rubella viruses); Flaviridae (e.g., dengue viruses, encephalitis viruses, yellow fever viruses); Coronaviridae (e.g., coronaviruses); Rhabdoviridae (e.g., vesicular stomatitis viruses, rabies viruses); Filoviridae (e.g., ebola viruses); Paramyxoviridae (e.g., parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (e.g. influenza viruses); Bungaviridae (e.g., Hantaan viruses, bunga viruses, phleboviruses and Nairo viruses); Arena viridae (hemorrhagic fever viruses); Reoviridae (erg., reoviruses, orbiviurses and rotaviruses); Birnaviridae; Hepadnaviridae (Hepatitis B virus); Parvoviridae (parvoviruses); Papovaviridae (papilloma viruses, polyoma viruses); Adenoviridae (most adenoviruses); Herpesviridae (herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytomegalovirus (CMV), herpes viruses'); Poxviridae (variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (e.g. African swine fever virus); and unclassified viruses (e.g., the etiological agents of Spongiform encephalopathies, the agent of delta hepatities (thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1=internally transmitted; class 2=parenterally transmitted (i.e., Hepatitis C); Norwalk and related viruses, and astroviruses).

Detailed Description Paragraph Right (40):
Unmethylated immunostimulatory CpG motifs, either within a nucleic acid construct or an oligonucleotide, directly activate lymphocytes and co-stimulate antigen-specific responses. As such, they are fundamentally different form aluminum precipitates (alum), currently the only adjuvant licensed for human use, which is thought to act largely through adsorbing the antigen thereby maintaining it available to immune cells for a longer period. Further, alum cannot be added to all types of antigens (e.g. live attentuated pathogens, some multivalent vaccines), and it induces primarily Th2 type immune responses, namely humoral inmmunity but rarely CTL. For many pathogens, a humoral response alone is insufficient for protection, and for some pathogens can even be detrimental.

Detailed Description Paragraph Right (52):
Various viral vectors which can be utilized for gene therapy as taught herein include adenovirus, herpes virus, vaccinia, or, preferably, an RNA virus such as a retrovirus. Preferably, the retroviral vector is a derivative of a murine or avian retrovirus. Examples of retroviral vectors in which a single foreign gene can be inserted include, but are not limited to: Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), and Rous Sarcoma Virus (RSV). When the subject is a human, a vector such as the gibbon ape leukemia virus (GaLV) can be utilized. A number of additional retroviral vectors can incorporate multiple genes. All of these vectors can transfer or incorporate a gene for a selectable marker so that transduced cells can be identified and generated.

Detailed Description Paragraph Right (58):
Administration of gene therapy vectors to a subject, either as a plasmid or as part of a viral vector can be affected by many different routes. Plasmid DNA can be "naked" or formulated with cationic and neutral lipids (liposomes), microencapsulated, or encochleated for either direct or indirect delivery. The DNA sequences can also be contained within a viral (e.g., adenoviral, retroviral, herpesvius, pox virus) vector, which can be used for either direct or indirect delivery. Delivery routes include but are not limited to intramuscular, intradermal (Sato, Y. et al., Science 273: 352-354, 1996), intravenous, intra-arterial, intrathecal, intrahepatic, inhalation,

intravaginal instillation (Bagarazzi et al., J Med. Primatol. 26:27, 1997), intrarectal, intratumor or intraperitoneal.

Detailed Description Paragraph Right (60):
Delivery of polynucleotides can be achieved using a plasmid vector as described herein, that can be administered as "naked DNA" (i.e., in an aqueous solution), formulated with a delivery system (e.g., liposome, cochelates, microencapsulated). Delivery of polynucleotides can also be achieved using recombinant expression vectors such as a chimeric virus. Thus the invention includes a nucleic acid construct as described herein as a pharnaceutical composition useful for allowing transfection of some cells with the DNA vector such that a therapeutic polypeptide will be expressed and have a therapeutic effect (to ameliorate symptoms attributable to infection or disease). The pharmaceutical compositions according to the invention are prepared by bringing the construct according to the present invention into a form suitable for administration to a subject using solvents, carriers, delivery systems, excipients, and additives or auxiliaries. Frequently used solvents include sterile water and saline (buffered or not). One carrier includes gold particles, which are delivered biolistically (ie., under gas pressure). Other frequently used carriers or delivery systems include cationic liposomes, cochleates and microcapsules, which may be given as a liquid solution, enclosed within a delivery capsule or incorporated into food.

Detailed Description Paragraph Right (61):
An alternative formulation for the administration of gene therapy vectors involves liposomes. Liposome encapsulation provides an alternative formulation for the administration of polynucleotides and expression vectors. Liposomes are microscopic vesicles that consist of one or more lipid bilayers surrounding aqueous compartments. See, generally, Bakker-Woudenberg et al, Eur. J. Clin. Microbiol. Infect. Dis. 12 (Suppl. 1): S61 (1993), and Kim, Drugs 46: 618 (1993). Liposomes are similar in composition to cellular membranes and as a result, liposomes can be administered safely and are biodegradable. Depending on the method of preparation, liposomes may be unilamellar or multilamellar, and liposomes can vary in size with diameters ranging from 0.02 .mu.m to greater than 10 .mu.m. See, for example, Machy et al., LIPOSOMES IN CELL BIOLOGY AND PHARMACOLOGY (John Libbey 1987), and Ostro et al., American J. Hosp. Phann. 46: 1576 (1989).

Detailed Description Paragraph Right (62):
After intravenous administration, conventional liposomes are preferentially phagocytosed into the reticuloendothelial system. However, the reticuloendothelial system can be circumvented by several methods including saturation with large doses of liposome particles, or selective macrophage inactivation by pharmacological means. Claassen et al., Biochim. Biophys. Acta 802: 428 (1984). In addition, incorporation of glycolipid- or polyethelene glycol-derivatised phospholipids into liposome membranes has been shown to result in a significantly reduced uptake by the reticuloendothelial system. Allen et al., Biochim. Biophys. Acta 1068: 133 (1991); Allen et al., Biochim. Biohys. Acta 1150: 9 (1993). These Stealth.RTM. liposomes have an increased circulation time and an improved targeting to tumors in animals. (Woodle et al., Proc. Amer. Assoc. Cancer Res. 33: 2672 1992). Human clinical trials are in progress, including Phase III clinical trials against Kaposi's sarcoma. (Gregoriadis et al., Drugs 45: 15, 1993).

Detailed Description Paragraph Right (63):
Expression vectors can be encapsulated within liposomes using standard techniques. A variety of different liposome compositions and methods for synthesis are known to those of skill in the art. See, for example, U.S. Pat. No. 4,844,904, U.S. Pat. No. 5,000,959, U.S. Pat. No. 4,863,740, U.S. Pat. No. 5,589,466, U.S. Pat. No. 5,580,859, and U.S. Pat. No. 4,975,282, all of which are hereby incorporated by reference.

Detailed Description Paragraph Right (64):
Liposomes can be prepared for targeting to particular cells or organs by varying phospholipid composition or by inserting receptors or ligands into the liposomes. For instance, antibodies specific to tumor associated antigens may be incorporated into liposomes, together with gene therapy vectors, to target the liposome more effectively to the tumor cells. See, for example, Zelphati et al., Antisense Research and Development 3: 323-338 (1993), describing the use "immunoliposomes" containing vectors for human therapy.

Detailed Description Paragraph Right (88):
Insertion of murine-specific CpO-S motifs was carnied out by first synthesizing the oligonucleotide 5' GAC TCC ATG ACG TTC CTG ACG TTT CCA TGA CGT TCC TGA CGT TG 3' (SEQ ID NO: 12) which contains four CpG-S motifs (underlined), and its complementary sequence 5' GTC CAA CGT CAG GAA CGT CAT GGA AAC GTC AGG AAC GTC ATG GA 3' (SEQ ID NO:13). This sequence is based on the CpG-S motifs contained in oligo #1826, which has potent stimulatory effects on murine cells in vitro and is a potent adjuvant for protein vaccines in vivo. After 5'-phosphorylation, annealing was performed to create a 44 bp double-stranded DNA fragment with AvaII-cut sticky ends. Self-ligation of this 44 bp DNA fragment resulted in a mixture of larger DNA fragments containing different copy numbers of the stimulatory motif These DNA fragments with different numbers of mouse CpG-S motifs were inserted into the AvaII site of pMAS, which was first dephosphorylated with CIP to prevent self-ligation. The resulting recombinant plasmids maintained one AvaII site due to the design of the synthetic oligonucleotide sequence allowing the cloning process to be repeated until the desired number of CpG-S motifs were inserted. Sixteen and 50 mouse CpG-S motifs were inserted into the AvaHi site of pMAS, creating pMCG-16 and pMCG-50 respectively. The DNA fragment containing 50 CpG-S motifs was excised from pMCG-50, and inserted into HpaI-AvaII-ScaI-DraI linker of pMCG-50, creating pMCG-100. The same procedure was followed to create pMCG-200 (Table 3). Two different sequences containing human-specific CpG-S motifs were cloned in different numbers into pMAS to create two series of vectors, pHCG and pHIS, following the same strategies as described above.

Detailed Description Paragraph Right (89):
The pHCG series of vectors contain multiple copies of the following sequence 5' GAC TTC GTG TCG TTC TTC TGT CGT CTT TA TTC TCC TGC GTG CGT CCC TTG 3' (SEQ ID NO:14) (CpG-S motifs are underlined). This sequence incorporates various CpG-S motifs that had previously been found to have potent stimulatory effects on human cells in vitro. The vector pHCG-30, pHCG-50, pHCG-100 and pHCG-200 contain 30, 50, 100 and 200 human CpG-S motifs respectively (Table 3).

Detailed Description Paragraph Right (90):
The pHIS series of vectors contain multiple copies of the following sequence: 5' GAC TCG TCG TTT TGT CGT TTT GTC GTT TCG TCG TTT TGT CGT TTT GTC GTT G 3' (SEQ ID NO: 15) (CPG-S motifs are underlined). This sequence is based on the CpG-S motifs in oligo #2006, which has potent stimulatory effects on human cells in vitro The vector pHIS-40, pHIS-64, pHIS-1 28 and pHIS-1 92 contain 40, 64, 128 and 192 human CpG motifs respectively (Table 3).

Detailed Description Paragraph Right (96):
Human CpG-N motifs were cloned into the pGTU following the same strategies as described previously in (iv) Insertion of immunostimulatory motifs into the vector pMAS. The oligonucleotide 5' GCC CTG GCG GGG ATA AGG CGG CGA TTT CGC GGG GGA TAA GGC GGG GAA 3' (SEQ ID NO:18) and its complementary strand 5' GGC CCC CGC CTT ATC CCC GCC AAA TCC CCG CCT TAT CCC CGC CAG 3' (SEQ ID NO:19) (four CpG motifs are underlined) were synthesized and phosphorylated. Annealing of these two oligonucleotides created a double-stranded DNA fragment, which was self-ligated first and then cloned into the EcoO109I site of the vector pGTU. The recombinant plasmids will be screened by restriction enzyme digestion and the vectors with the desired number of CpG inhibitory motifs will be sequenced and tested.

Detailed Description Paragraph Right (97):
Female BALB/c mice aged 6-8 weeks (Charles River, Montreal) were immunized with DNA vaccines of HBsAg-encoding DNA (see vectors described above) by intramuscular injection into the tibialis anterior (TA) muscle. The plasmid DNA was produced in E. coli and purified using Qiagen endotoxin-free DNA purification mega columns (Qiagen GmbH, Chatsworth, Calif.). DNA was precipitated and redissolved in endotoxin-free PBS (Sigma, St. Louis MO) at a concentration of 0.01, 0.1 or 1 mg/ml. Total doses of 1, 10 or 100 .mu.g were delivered by injection of 50 .mu.l bilaterally into the TA muscles, as previously described (Davis et al., 1993b).

Detailed Description Paragraph Right (102):
Unlike the genome of almost all DNA viruses and retroviruses, some adenoviral genomes do not show suppression of CpG dinucleotides (Karlin et al., 1994; Sun et al., 1997).

Analysis of different adenoviral genomes (types 2, 5, 12, and 40) reveals surprising variability among each other and compared to human and E. coli in the flanking bases around CpG dinucleotides (Table 7).

Detailed Description Paragraph Right (103):
Adenoviral strains 2 and 5 belong to the same family but strain 12 is quite distinct from them. Purified type 12 adenoviral DNA induced cytokine secretion from human PBMC to a degree similar to that seen with bacterial DNA (EC DNA) (Table 8). In contrast, DNA from types 2 and 5 adenoviruses induced little or no production of cytokines (Tables 3, 4). Remarkably, not only did type 2 and 5 adenoviral DNA fail to induce TNF-.alpha. or IFN-.gamma. secretion, it actively inhibited the induction of this secretion by EC DNA (Table 9). In contrast, type 12 adenoviral DNA had no discernible inhibitory effects. These data suggested that type 2 and 5 adenoviral DNA contains sequence motifs that inhibit the cytokine responses to the stimulatory motifs present.

Detailed Description Paragraph Right (104):
The bases flanking CpG motifs determine whether a CpG dinucleotide will cause immune stimulation, and may also determine the type of cytokines secreted. The fact that type 2 and 5 adenoviral DNA was not only nonstimulatory but actually inhibitory of CpG DNA, suggested that certain nonstimulatory CpG motifs may even be able to block the stimulatory motifs and that the inhibitory motifs should be over-represented in the genomes of adenovirus type 2 and 5 compared to type 12 (or to human DNA). By analysis of these genomes, it was possible to identify sequences that could block the effects of known CpG-S sequences on in vitro B cell proliferation (Table 10) and cytokine secretion (Table 11).

Detailed Description Paragraph Right (114):
Construction of optimized DNA vectors. The starting material was pUK21-A2, an expression vector containing the immediate early promoter of human cytomegalovirus (CMV IE), the bovine growth hormone (BGH) polyadenylation signal, and the kanamycin resistance gene (Wu and Davis, unpublished). To avoid disrupting the plasmid origin of replication, mutagenesis designed to eliminate CpG-N motifs was restricted to the kanamycin resistance gene and non-essential DNA sequences following the gene. A total of 22 point mutations were introduced to alter 15 CpG-N motifs (a "motif" refers to a hexamer containing one or more CpG dinucleotides) containing 19 CpG dinucleotides, 12 of which were eliminated and 7 of which were transformed into CpG-S motifs. Site-directed mutagenesis was performed by overlap extension PCR as described by Ge et aL (Prosch, S., et al., Biol. Chem., 377, 195-201 (1996)). The 1.3 kb AlwN I-Eco0109I fragment of pUK21-A2, which contained all 22 nucleotides to be mutated, was used as the template for PCR. The 1.3 kb fragment was regenerated by four rounds of overlap extension PCR using appropriate mutagenic primers, and substituted for the original AlwN I-Eco0109I fragment, resulting in pUK21-B2. All the mutations were confirned by sequencing.

Detailed Description Paragraph Right (119):
Type 12 adenoviral DNA is immune stimulatory, but types 2 and 5 adenoviral DNA are immune neutralizing. To investigate possible functional differences in the immune effects of various prokaryotic DNAs, we determined their ability to induce cytokine secretion from human PBMC. In contrast to bacterial DNA and genomic DNA from type 12 adenovirus, DNA from types 2 and 5 adenovirus failed to induce cytokine production (Table 8). In fact, despite their similar frequency of CpG dinucleotides, type 2 or 5 adenoviral DNA severely reduced the cytokine expression induced by co-administered immunostimulatory E. coli genomic DNA (Table 9). This indicates that type 2 and 5 adenoviral DNA does not simply lack CpG-S motifs, but contains sequences that actively suppress those in E. coli DNA.

Detailed Description Paragraph Right (120):
Identification of putative immune neutralizing CpG-N motifs in type 2 and 5 adenoviral genomes. To identify possible non-random skewing of the bases flanking the CpG dinucleotides in the various adenoviral genomes, we examined their frequency of all 4096 hexamers. The six most common hexamers in the type 2 adenoviral genome are shown in Table 7, along with their frequency in the Type 12 and E. coli genomes. Remarkably, all of these over-represented hexamers contain either direct repeats of CpG dinucleotides, or CpGs that are preceded by a C and/or followed by a G. These CpG-N

motifs are approximately three to six fold more common in the inunune inhibitory type 2 and 5 adenoviral genomes than in those of immune-stimulatory type 12 adenoviral, E. coli or non-stimulatory human genomic DNAs (Table 7). This hexamer analysis further revealed that the frequency of hexarners containing CpG-S motifs (e.g., GACGTT or AACGTT) in the type 2 adenoviral genome is as low as that in the human genome: only 1/3 to 1/6 of that in E. coli and type 12 adenoviral DNA (Table 7).

Detailed Description Paragraph Right (127):
CpG-N motifs are also over-represented in the human genome, where their hexamers are approximately two to five-fold more common than CPG-S motifs. While this skewing is far less marked than that in adenoviral DNA, it would still be expected to reduce or eliminate any immune stimulatory effect from the unmethylated CpGs present in CpG islands within vertebrate DNA. We and others have found that even when predominantly or completely unmethylated, vertebrate DNA is still not immune stimulatory (A. Krieg and P. Jones, unpublished data) (Sun, S., et al., J. Immunol., 159:3119-3125 (1997)) which is in keeping with its predominance of CpG-N motifs (Table 7). Given the overall level of CpG suppression in the human genome, the molecular mechanisms responsible for the skewing of the frequency of CpG-N to CpG-S motifs are unclear. Such a distortion from the expected random patterns would seem to require the existence of pathways that preferentially mutate the flanking bases of CPG-S motifs in vertebrate genomes, but do not affect CPG-N motifs. Indeed, statistical analyses of vertebrate genomes have provided evidence that CpGs flanked by A or T (as in CpG-S motifs) mutate at a faster rate than CpGs flanked by C or G (Bains, W., et al., Mutation Res., 267:43-54 (1992)).

Detailed Description Paragraph Right (131):
In recent years, it has become clear that effective gene expression need not require a viral delivery system. The use of plasmids for gene delivery (with or without lipids or other formulations) avoids some of the problems of viral vectors. On the other hand, much larger doses of DNA are typically required, since delivery is far less efficient than with a targeted system such as a virus. For example, effective gene expression in mice typically may require 500-1000 .mu.g DNA/mouse (Philip, R., et al., J. Biol. Chem., 268:16087-16090 (1993); Wang, C., et al., J. Clin. Invest., 95:1710-1715 (1995)). A recent human clinical trial using lipid/DNA complexes and naked DNA for delivery of CFTR to the nasal epithelium of patients with cystic fibrosis used doses of 1.25 mg of plasmid/nostril (Zabner, J., et al., J Clin. Invest., 100:1529-1537 (1997)). The successful application of naked DNA expression vectors for gene therapy will depend on the safety of repeatedly delivering high doses of DNA. Since the plasmids used for gene therapy typically contain several hundred unmethylated CpG dinucleotides, many of which are in CpG-S motifs, some immune activation may be expected to occur. Indeed, mice given repeated doses of just 10 .mu.g of plasmid DNA daily develop elevated lymphocyte levels and several humans who received intranasal plasmid DNA had elevated serum IL-6 levels (Philip, R., et al., J. Biol Chem., 268:16087-16090 (1993)). Furthermore, delivery of 4 mg of a gene therapy plasmid to cystic fibrosis patients in a recent clinical trial caused acute onset of symptoms compatible with immune activation, including fever, chills, and pulmonary congestion. Another reason to avoid the presence of CpG-S motifs in gene therapy vectors is that the cytokines that are produced due to the immune stimulation may reduce plasmid vector expression, especially when this is driven by viral promoters (Raz, E., et al., Proc. Natl. Acad. Sci. USA, 93:5141-5145 (1996)).

Detailed Description Paragraph Right (136):
The frequencies of hexamers in adenoviral and E. coli genomes were kindly provided by J. Han (University of Alabama, Birmingham), who also determined those for the human genome.sup.52. The hexamer frequencies in type 5 adenovirus are essentially identical to those in type 2, and are therefore not shown. The last two hexamers are CpG-S motifs shown for comparison and are the most stimulatory of all tested CpG-S motifs.

Detailed Description Paragraph Left (3):
Delivery of polynucleotides can be achieved using a plasmid vector as described herein, that can be administered as "naked DNA" (i.e., in an aqueous solution), formulated with a delivery system (e.g., liposome, cochelates, microencapsulated), or coated onto gold particles. Delivery of polynucleotides can also be achieved using recombinant expression vectors such as a chimeric virus. Thus the invention includes a nucleic acid construct as described herein as a pharmaceutical composition useful for

allowing transfection of some cells with the DNA vector such that antigen will be expressed and induce a protective (to prevent infection) or a therapeutic (to ameliorate symptoms attributable to infection or disease) immune response. The pharmaceutical compositions according to the invention are prepared by bringing the construct according to the present invention into a form suitable for administration to a subject using solvents, carriers, delivery systems, excipients, and additives or auxiliaries. Frequently used solvents include sterile water and saline (buffered or not). A frequently used carrier includes gold particles, which are delivered biolistically (i.e., under gas pressure). Other frequently used carriers or delivery systems include cationic liposomes, cochleates and microcapsules, which may be given as a liquid, solution, enclosed within a delivery capsule or incorporated into food.

Detailed Description Paragraph Left (10):
(i) Insertion of the CMV (human cytomegalovirus) major intermediate early promoter/enhancer region

Detailed Description Paragraph Left (25):
Human PBMC were cultured in 96 well microtiter plates at 10.sup.5 /200 .mu.l for 24 hr in RPMI containing 10% autologous serum. Supernatants were collected at the end of the culture and tested for IL-12 by ELISA. All wells except the control (medium) contained 60 .mu.g/ml of the stimulatory CpG oligodeoxynucleotide 1619; stimulatory (1949) and inhibitory (all other sequences have a strong inhibitory motif) oligos were added to the indicated wells at the same concentration at the beginning of culture. All oligos have unmodified backbones.

Detailed Description Paragraph Type 0 (11):
Intramuscular delivery of DNA vaccines

Detailed Description Paragraph Type 0 (12):
Davis, H. L., Michel, M.-L., Whalen, R. G. (1993b) DNA based immunization for hepatitis B induces continuous secretion of antigen and high levels of circulating antibody. Human Molec. Genet., 2, 1847-1851.

Detailed Description Paragraph Type 0 (13):
Yankauckas, M. A., Morrow, J. E., Parker, S. E., Abai, A., Rhodes, G. H., Dwarki, V. J., Gromkowski, S. H. (1993) Long-term anti-nucleoprotein cellular and humoral immunity is induced by intramuscular injection of plasmid DNA containing NP gene. DNA Cell Biol., 12, 771-776.

Detailed Description Paragraph Type 0 (16):
Bagarazzi, M. L., Boyer, J. D., Javadian, M. A., Chattergoon, M., Dang, K., Kim, G., Shah, J., Wang, B., & Weiner, D. B. (1997). Safety and immunogenicity of intramuscular and intravaginal delivery of HIV-1 DNA constructs to infant chimpanzees. J. Med. Primatol., 26, 27-33. intranasal

Detailed Description Paragraph Type 0 (25):
Doe, B., Selby, S., Barnett, J., Baenziger, J., & Walker, C. M. (1996). Induction of cytotoxic T lymphocytes by intramuscular immunization with plasmid DNA is facilitated by bone marrow-derived cells. Proc. Natl. Acad. Sci. USA, 93, 8578-8583.

Detailed Description Paragraph Type 0 (30):
Michel, M. L., Davis, H. L., Schleet M., Mancini, M., Tiollais, P., & Whalen, R. G. (1995). DNA-mediated immunization to the hepatitis B surface antigen in mice: Aspects of the humoral response mimic hepatitis B viral infection in humans. Proc. Natl. Acad. Sci. USA, 92, 5307-5311.

Detailed Description Paragraph Type 0 (37):
Conry, R. M., LoBuglio, A. F., Loechel, F., Moore, S. E., Sumerel, L. A., Barlow, D. L., Pike, J., Curiel D. T. (1995) A carcinoembryonic antigen polynucleotide vaccine for human clinical use. Cancer Gene Ther., 2, 33-38.

Detailed Description Paragraph Type 0 (41):
Ballas, Z. K., Rasmussen, W. L. and Krieg, A. M. Induction of natural killer activity in murine and human cells by CpG motifs in oligodeoxynucleotides and bacterial DNA. J. Immunol. 157: 1840-1845 (1996).

Detailed Description Paragraph Type 0 (42):
Bartlett, R. J., Secore, S. L., Singer, J. T., Bodo, M., Sharma, K. and Ricordi, C. Long-term expression of a fluorescent reporter gene via direct injection of plasmid vector into mouse skeletal muscle: comparison of human creatine kinase and CMV promoter expression levels in vivo. Cell Transplantation. 5: 411-419 (1996).

Detailed Description Paragraph Type 0 (46):
Davis, H. L., Michel, M. -L. and Whalen, R. G. DNA based immunization for hepatitis B induces continuous secretion of antigen and high levels of circulating antibody. Human Molec. Genetics. 2: 1847-1851 (1993a).

Detailed Description Paragraph Type 0 (47):
Davis H. L., Whalen R. G. and Demeneix B. A. Direct gene transfer into skeletal muscle in vivo: factors affecting efficiency of transfer and stability of expression. Human Gene Ther. 4: 151-159 (1 993b).

Detailed Description Paragraph Type 0 (57):
Harms, J. S. and Splitter G. A. Interferon-gamma inhibits transgene expression driven by SV40 or CMV promoters but augments expression driven by the mammalian MHC I promoter. Human Gene Ther. 6: 1291-1297 (1995).

Detailed Description Paragraph Type 0 (58):
Horvath, J., Palkonyay, L. and Weber, J. Group C adenovirus DNA sequences in human lymphoid cells. J. Virol. 59: 189-192 (1986).

Detailed Description Paragraph Type 0 (68):
Miller, A. D. Human gene therapy comes of age. Nature. 357: 455-460 (1992).

Detailed Description Paragraph Table (3):
TABLE 3 Plasmids containing immunostimulatory CpG motifs Species Specificity and No. CpG, ODN Equivalence of CpG-S Plasmid Backbone Motifs Insert pMCG-16 pMAS 16 mouse-specific CpG motif pMCG-50 pMAS 50 #1826.sup.1 pMCG-100 pMAS 100 pMCG-200 pMAS 200 pHCG-30 pMAS 30 human-specific CpG motif - pHCG-50 pMAS 50 no ODN equivalent.sup.2 pHCG-100 pMAS 100 pHCG-200 pMAS 200 pHIS-40 pMAS 40 human-specific CpG motif pHIS-64 pMAS 64 #2006.sup.3 pHIS-128 pMAS 128 pHIS-192 pMAS 192 .sup.1 sequence of 1826 is TCCATGACGTTCCTGACGTT .sup.2 sequence used as a source of CpG motifs is GACTTCGTGTCGTTCTTCTGTCGTCTTTAGCGCTTCTCCTGCGTGCGTCCCTTG(SEQ ID NO:14) .sup.3 sequence of 2006 is TCGTCGTTTTGTCGTTTTGTCGTT(SEQ ID NO:3)

Detailed Description Paragraph Table (8):
TABLE 7 Genomic frequencies of selected hexamers Genomic frequency (.times.10.sup.-3) Adenovirus Adenovirus hexamer: Type 2 Type 12 E. coli Human GCGCGC 1.614 0.498 0.462 0.153 GCGGCG 1.530 0.469 0.745 0.285 GGCGGC 1.419 0.440 0.674 0.388 CGCGCG 1.336 0.322 0.379 0.106 GCCGCC 1.280 0.410 0.466 0.377 CGCCGC 1.252 0.410 0.623 0.274 GACGTT 0.083 0.234 0.263 0.068 AACGTT 0.056 0.205 0.347 0.056 (CpG-S)

Detailed Description Paragraph Table (9):
TABLE 8 Genomic DNA from type 12 but not type 2 adenovirus stimulates cytokine secretion from human PBMC Experiment 1.sup.1 Experiment 2.sup.1 TNF-.alpha. IL-6 TNF-.alpha. IL-6 Cells 27 800 30 800 EC 3 .mu.g/ml 235 26,500 563 34,000 CT 10 .mu.g/ml 0 1,400 0 2,800 Adv 2;3 .mu.g/ml 15.6 900 30 1,900 Adv 12;3 .mu.g/ml 86 11,300 120 11,250 .sup.1 PBMC were obtained from normal human donors and cultured at 1 .times. 10.sup.5 cells/200 .mu.l in RPMI with 10% autologous serum for 4 hr (TNF-.alpha. assay) or 24 hr (IL-6 assay). The level of cytokine present in culture supernatants was determined by ELISA (pg/ml). Adv = adenovirus serotype

Detailed Description Paragraph Table (10):
TABLE 9 Adenoviral type 5 DNA suppresses the cytokine response to EC DNA by human PBMC IL-6 DNA Source (pg/ml).sup.1 IFN-(pg/ml).sup.1 TNF-(pg/ml).sup.1 EC DNA(50 .mu.g/ml) >3000 700 700 EC DNA(5 .mu.g/ml) >3000 400 675 EC DNA(0.5 .mu.g/ml) >3000 200 350 EC DNA(0.05 .mu.g/ml) 3000 ND 100 Adenoviral DNA (50 .mu.g/ml) 2500 0 0 Adenoviral DNA (5 .mu.g/ml) 1500 0 0 EC:Adeno DNA(50:50 2000 35 675 .mu.g/ml) EC:Adeno DNA (5:5 .mu.g/ml) 1500 40 ND .sup.1 Represents the level of cytokine production above that in wells cultured with cells alone without any DNA. Levels of cytokines were determined

by ELISA using Quantikine kits from R & D Systems. ND = not done

Other Reference Publication (2):
Anderson, Human Gene therapy, Nature vol. 392, Apr. 30, 1998, pp. 25-30.*

Other Reference Publication (7):
Cox GJM et al. Bovine herpesvirus 1: immune responses in mice and cattle injected with plasmid DNA. J Virol Sep. 1993; 67(9):5664-7.

Other Reference Publication (10):
Parker SE et al. Plasmid DNA gene therapy: studies with the human interleukin-2 gene in tumor cells in vitro and in the murine B16 melanoma model in vivo. Cancer Gene Therapy May-Jun. 1996; 3(3):175-85.

Other Reference Publication (13):
Wang B et al. Gene inoculation generates immune responses against human immunodeficiency virus type I. Proc Natl Acad Sci USA May 1993; 90:4156-60.

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Wloch MK et al. The influence of DNA sequence on the immunostimulatory properties of plasmid DNA vectors. Human Gene Therapy Jul. 1, 1998; 1439-47.

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Azad RF et al., Antiviral activity of a phosphorothioate oligonucleotide complementary to RNA of the human cytomegalovirus major immediate-early region. Antimicrobial Agents and Chemotherapy, 37:1945-1954, Sep., 1993.

Other Reference Publication (23):
Ballas ZK et al., Induction of NK activity in murine and human cells by CpG motifs in oligodeoxynucleotides and bacterial DNA. J Immunol 157(5):1840-5, 1996.

Other Reference Publication (25):
Bennett RM et al., DNA binding to human leukocytes. Evidence for a receptor-mediated association, internalization, and degradation of DNA. J Clin Invest 76(6):2182-90, 1985.

Other Reference Publication (42):
D'Andrea A et al., Interleukin 10 (IL-10) inhibits human lymphocyte interferon gamma-production by suppressing natural killer cell stimulatory factor/IL-12 synthesis in accessory cells. J Exp Med 178(3):1041-8, 1993.

Other Reference Publication (48):
Doe B et al., Induction of cytotoxic T lymphocytes by intramuscular immunization with plasmid DNA is facilitated by bone marrow-derived cells. Proc Natl Acad Sci USA 93:8578-8583, 1996.

Other Reference Publication (61):
Hatzfeld J et al., Release of early human hematopoietic progenitors from quiescence by antisense transforming growth factor .beta.1 or Rb oligonucleotides. J Exp Med 174:925-929, 1991.

Other Reference Publication (67):
Iversen P et al., Pharmacokinetics of an antisense phosphorothioate oligodeoxynucleotide against rev from human immunodeficiency virus type 1 in the adult male rate following single injections and continuous infusion. Antisense Res Dev 4:43-52, 1994.

Other Reference Publication (90):
Liu MA et al., Immunization of non-human primates with DNA vaccines. Vaccine 15(8):909-12, 1997.

Other Reference Publication (93):
Mastrangelo MJ et al., Gene therapy for human cancer. Seminars in Oncology 23(1):4-21, 1996.

Other Reference Publication (141):
Yamamoto T et al., Synthetic oligonucleotides with certain palindromes stimulate interferon production of human peripheral blood lymphocytes in vitro. Jpn J Cancer Res 85:775-779, 1994.

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Yaswen P et al., Effects of sequence of thioated oligonucleotides on cultured human mammary epithelial cells. Antisense Res Dev 3(1):67-77, 1993.

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TITLE: Methods of treating disease using recombinant adeno-associated virus virions administered to muscle

DATE-ISSUED: December 4, 2001

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/93.2; 424/93.6, 435/320.1, 514/44

CLAIMS:

What is claimed is:

1. A method of expressing a selected gene in muscle cells present in a mammalian subject, said method comprising:

(a) providing recombinant adeno-associated virus (AAV) virions, wherein said virions are free of both wild-type AAV and infectious helper virus, and wherein said virions comprise an AAV vector, said AAV vector comprising said selected gene operably linked to control elements that direct the in vivo transcription and translation of said selected gene in the muscle cells; and

(b) delivering said recombinant AAV virions directly to said muscle cells, whereby said selected gene is expressed at a level which provides a therapeutic effect in the mammalian subject.

2. The method of claim 1, wherein said muscle cells are derived from skeletal muscle.

3. The method of claim 1, wherein said muscle cells are derived from smooth muscle.

4. The method of claim 1, wherein said muscle cells are derived from cardiac muscle.

5. The method of claim 1, wherein said muscle cells are skeletal myoblasts.

6. The method of claim 1, wherein said muscle cells are skeletal myocytes.

7. The method of claim 1, wherein said muscle cells are cardiomyocytes.

8. The method of claim 1, wherein said selected gene encodes a therapeutic protein.

9. The method of claim 8, wherein said protein is erythropoietin.

10. A method of treating a disease in a mammalian subject, said method comprising:

administering directly into muscle of said subject a therapeutically effective amount of a pharmaceutical composition which comprises (a) a pharmaceutically acceptable excipient; and (b) recombinant AAV virions free of both wild-type AAV and infectious

helper virus, wherein said virions comprise an AAV vector, said AAV vector comprising a selected gene operably linked to control elements that direct the transcription and translation of said selected gene when present in muscle cells in said subject, whereby said virions transduce muscle cells in said subject, and said selected gene is expressed by said transduced cells at a level sufficient to treat the disease.

11. A method of treating disease in a mammalian subject, said method comprising:

(a) introducing recombinant AAV virions free of both wild-type AAV and helper virus into muscle cells in vitro to produce a population of transduced muscle cells, wherein said recombinant AAV virions comprise an AAV vector containing a selected gene operably linked to control elements that direct the transcription and translation of said selected gene when present in said subject; and

(b) administering to muscle of said subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable excipient and the transduced muscle cells from step (a), whereby said selected gene is expressed by said transduced cells at a level sufficient to treat the disease.

12. A method for delivering a therapeutically effective amount of a protein systemically to a mammalian subject, said method comprising:

administering directly into muscle of said subject a pharmaceutical composition which comprises (a) a pharmaceutically acceptable excipient; and (b) recombinant AAV virions free of both wild-type AAV and infectious helper virus, wherein said virions comprise an AAV vector, said AAV vector comprising a selected gene operably linked to control elements that direct the transcription and translation of said selected gene when present in said subject, whereby said virions transduce muscle cells in said subject, and said selected gene is expressed by the transduced cells to produce a systemic level of the protein which provides for a therapeutic effect in said subject.

13. A method for delivering a therapeutically effective amount of a protein systemically to a mammalian subject, said method comprising:

(a) introducing recombinant AAV virions free of both wild-type AAV and infectious helper virus into muscle cells in vitro to produce a population of transduced muscle cells, wherein said recombinant AAV virions comprise an AAV vector containing a selected gene operably linked to control elements that direct the transcription and translation of said selected gene when present in said subject; and

(b) administering to muscle of said subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable excipient and the transduced muscle cells from step (a), whereby said selected gene is expressed by said transduced cells to produce a systemic level of the protein which provides for a therapeutic effect in said subject.

14. A method of secreting protein from muscle cells present in a mammalian subject, said method comprising:

(a) providing recombinant adeno-associated virus (AAV) virions free of both wild-type AAV and infectious helper virus wherein said virions comprise an AAV vector having a gene encoding said protein and operably linked to control elements which direct the in vivo transcription and translation of the gene in said muscle cells; and

(b) delivering the recombinant AAV virion directly to said muscle cells, whereby said protein is expressed and secreted from said muscle cells at a level which provides a therapeutic effect in the mammalian subject.

15. The method of claim 14, wherein said muscle cells are derived from skeletal muscle.

16. The method of claim 14, wherein said muscle cells are derived from smooth muscle.

17. The method of claim 14, wherein said muscle cells are derived from cardiac muscle.

18. The method of claim 14, wherein said muscle cells are skeletal myoblasts.

19. The method of claim 14, wherein said muscle cells are skeletal myocytes.

20. The method of claim 14, wherein said muscle cells are cardiomyocytes.

21. The method of claim 14, wherein said recombinant AAV virions are delivered in vivo.

22. The method of claim 21, wherein said recombinant AAV virions are delivered by intramuscular injection.

23. The method of claim 14, wherein said recombinant AAV virions are delivered to said muscle cells in vitro and said muscle cells are delivered directly into muscle of said subject.

24. The method of claim 14, wherein the protein is a therapeutic protein.

1: J Infect Dis 1998 Jul;178(1):1-7

Cervical antibody responses to a herpes simplex virus type 2 glycoprotein subunit vaccine.

Ashley RL, Crisostomo FM, Doss M, Sekulovich RE, Burke RL, Shaughnessy M, Corey L, Polissar NL, Langenberg AG.

University of Washington and The Mountain-Whisper-Light Statistical Consulting, Seattle 98105, USA.

Effective vaccines against genital herpes simplex virus type 2 (HSV-2) may need to induce genital tract immune responses. To determine local antibody responses to HSV-2 glycoproteins gB2 and gD2 in an intramuscular subunit vaccine, cervical secretions from HSV-seronegative women and HSV-1-seropositive women were tested for IgG and IgA to gB2 and gD2 by enhanced chemiluminescence Western blot. Most (94%) of the seronegative subjects developed cervical IgG to gB2, IgG to gD2, and IgA to gB2; 72% developed IgA to gD2. All HSV-1-seropositive subjects had cervical IgG responses to vaccine gB2 and gD2, 85% had IgA responses to gB2, and 50% had IgA responses to gD2. Responses were more rapid and titers more consistently sustained in the HSV-1-seropositive women. Further, vaccination resulted in cervical IgG and IgA titers comparable to those to HSV-2 gB2 and gD2 in response to recurrent HSV-2 genital infection.

PMID: 9652416 [PubMed - indexed for MEDLINE]

1: J Infect Dis 1987 May;155(5):921-30

Immunization of experimental animals with reconstituted glycoprotein mixtures of herpes simplex virus 1 and 2: protection against challenge with virulent virus.

Meignier B, Jourdier TM, Norrild B, Pereira L, Roizman B.

Artificial mixtures of the glycoproteins B, C, D, and E of herpes simplex virus 1 and 2 (HSV-1 and HSV-2), purified individually from infected Vero cell lysates by immunoaffinity to monoclonal antibodies, were bound to an aluminum hydroxide gel and were used to immunize mice, guinea pigs, and owl monkeys (Aotus trivirgatus) once or twice (mice and guinea pigs) to as many as four times (owl monkeys). In all animals tested, low levels of neutralizing antibodies were detected only after two or more immunizations. Lymphocyte transformation tests in owl monkeys suggested low or borderline levels of cellular immunity. The survival of immunized mice after intracerebral challenge was inversely related to the challenge dose. Immunized guinea pigs challenged by intravaginal inoculation showed reduced morbidity at the site of inoculation and were protected from CNS disease. Both immunized and nonimmunized monkeys were highly susceptible and could not be differentiated with respect to morbidity or mortality when challenged with 1,000 pfu of HSV-2 by the intravaginal route.

PMID: 3031174 [PubMed - indexed for MEDLINE]

1: Vaccine 1988 Oct;6(5):414-8 Related Articles, NEW **Books**, LinkOut

Erratum in:
- Vaccine 1989 Feb;7(1):77

Mucosal antibody response to vaginal infection with herpes simplex virus in pre-vaccinated guinea-pigs.

McBride BW, Ridgeway P, Phillpotts R, Newell DG.

Porton Products Ltd, Centre for Applied Microbiology and Research, Salisbury, Wiltshire, UK.

The mucosal antibody response, in female guinea-pigs vaccinated with the Skinner herpes simplex virus vaccine, has been investigated. The HSV-specific secretory IgA response was assessed using the cross-reactivity of an antiserum raised against human secretory component. Animals vaccinated subcutaneously at a distant site were shown to respond to subsequent infection with HSV by the production of HSV-specific vaginal IgG and secretory IgA. No vaginal HSV-specific antibodies were found in infected, non-vaccinated animals.

PMID: 2461621 [PubMed - indexed for MEDLINE]

Plasmid DNA expression systems for the purpose of immunization.

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DNA vaccines induce immune responses against antigens synthesized in vivo after direct introduction of the DNA's encoding sequences. This unique approach to immunization may overcome deficits of traditional antigen-based approaches and provide safe and effective prophylactic and therapeutic vaccines. DNA vaccines are also useful as a research tool, such as for production of monoclonal antibodies. Efforts are now focusing on understanding the mechanism of antigen presentation and the adjuvant effect of immunostimulatory CpG motifs in the vectors to aid optimization of DNA vaccines.

Publication Types:
- Review
- Review, Tutorial

PMID: 9353234 [PubMed - indexed for MEDLINE]